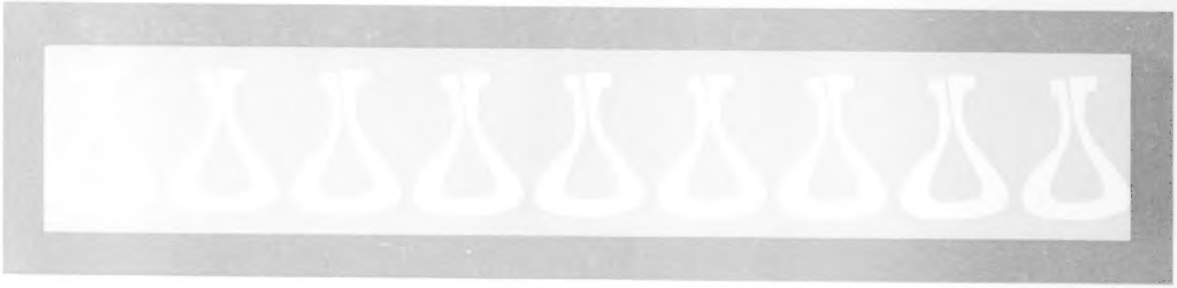

THE NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

VOL. 11 NO. 1—July 1973

PSYCHOPHARMACOLOGY ABSTRACTS

NATIONAL INSTITUTE OF MENTAL HEALTH

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In order to bring *Psychopharmacology Abstracts* up to currency as quickly as possible, the National Clearinghouse for Mental Health Information has taken the following actions: (1) A Supplement to Volume 10 is being issued containing approximately 2000 citations and (2) beginning with Volume 11, the journal will be issued on a quarterly basis. In this way it is expected that beginning with Issue 4 of Volume 11, abstracts will be announced as they are added to the NCMHI computer files regardless of publication date, making them as current as possible. We regret any inconvenience the time lag has caused our subscribers.

Effective with the first issue of Volume 11, the subscription price will be $16.90 for domestic mailing and $21.15 for foreign mailing.

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Carrie Lee Rothgeb, *Editor*
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ABSTRACTS

PRECLINICAL PSYCHOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

107672 Hornemann, K.M.Kelley; Neal, J.M.; McLaughlin, J.L. author address not given Cactus alkaloids XII: beta-phenethylamine alkaloids of the genus Coryphantha. ***Journal of Pharmaceutical Sciences.*** **61(1):41-45, 1972.**

The presence of alkaloids was chromatographically demonstrated in 7 species of Coryphantha. By using preparative chromatographic techniques, N-methyl-3, 4-dimethoxy-beta-phenethylamine, N-methyl-4-methoxy-beta-phenethylamine, N-methyltyramine, and N, N-dimethyltyramine (hordenine) were isolated from extracts of C.cornifera (DC.)Br.and R.var.echinus (Engelm.)L.Benson. In addition 2 new cactus alkaloids, beta-O-methylsynephrine (N-methyl-4-hydroxy-beta-methoxy-beta-phenethylamine) and 4-methoxy-beta-hydroxy-beta-phenethylamine, were identified spectroscopically in extracts of this species. 36 references. (Author abstract)

113976 Martin, W.R.; Sloan, J.W.; Christian, S.T.; Clements, T.H. NIMH Addiction Research Center, P.O.Box 2000, Lexington, Ky. 40507 Brain levels of tryptamine. ***Psychopharmacologia (Berlin).*** **24(3):331-346, 1972.**

A modification of the method of Hess and Udenfriend (1959) for the extraction and identification of tryptamine, as well as a gas chromatographic method for identifying tryptamine, has been described. Tryptamine, using these methods, as well as thin layer chromatography, has been identified in steer, dog and human brain. Tryptamine was not found in the rat brain. In the dog, isocarboxazid increased brain spinal cord typtamine levels 2 or 3 times. In view of the fact that tryptamine resembles LSD like hallucinogens in many of its actions, it is suggested that typtamine may be a naturally occurring hallucinogen that may play a role in normal and pathologic functioning of the brain. 23 references. (Author abstract)

115281 Breyer, U.; Krauss, D.; Jochims, J.C. Institut fur Toxikologie der Universitat, Wilhemstrasse 56, D-74 Tubingen, Germany A cumulating metabolite derived from a piperazine-substituted phenothiazine drug. ***Experientia (Basel).*** **28(3):312-313, 1972.**

Repeated application of a piperazine substituted phenothiazine drug, perazine, led to the accumulation of a previously unknown metabolite in tissues of rats. Mass spectrum investigation showed that this metabolite was identical to synthetically prepared N-(gamma-Phenothiazinyl-(10)-propyl)-ethylenediamine (PPED). In acute experiments with 50mg/kg perazine per os, PPED proved to be a minor metabolite in rat liver. Repeated dosages lead to a progressive increase in its tissue concentration. After termination of perazine administration, tissue levels of PPED declined much slower than those of other metabolites, and PPED was still detectable in various organs two weeks after the last dosage. It is concluded that the occurrence of PPA in rat liver showed that the piperazine ring can be completely degraded leaving only one amino group. 4 references.

115288 Wenkert, E.; Cochran, D.W.; Schell, F.M.; Archer, R.A.; Matsumoto, K. Department of Chemistry, Indiana University, Bloomington, IN 47401 CMR spectral analysis of tetrahydrocannabinol and its isomers. ***Experientia (Basel).*** **28(3):250-251, 1972.**

Chemical composition of the major psychotomimetic marihuana (hashish) principle tetrahydrocannabinol and its isomers are investigated by 13C nuclear magnetic resonance (cmr) spectroscopy. The delta values of all carbons of six tetrahydrocannabinol substances and olivetol dimethyl ether, derived from their noise resonance decoupled and single frequency decoupled spectra are listed. 8 references.

115292 Friedhoff, Arnold J.; Schweitzer, Jack W.; Miller, Jeannette. Millhouser Laboratories of the Department of Psychiatry, New York University School of Medicine, 550 First Avenue, New York, NY 10016 Biosynthesis of mescaline and N-acetylmescaline by mammalian liver. ***Nature (London).*** **237(5356):454-455, 1972.**

An enzyme in mammalian liver is shown to transform 4-desmethylmescaline (4-DMM) to mescaline (3,4,5-trimethoxy-beta-phenethylamine) and N-acetyl-4-desmethyl-mescaline (NA-4-DMM) to N-acetylmescaline. The mescaline forming enzyme is most active against substrates carrying the hydroxy substituent in the four position. The presence of both a 3- and a 5-methoxy substituent

on the favored mescaline precursor may have a strong directional effect on the O-methylating enzyme, which overcomes expected steric hindrance toward methylation of the 4 hydroxy group. Alternatively, mescaline and N-acetyl-mescaline may be formed by an enzyme different from that involved in the formation of the dimethoxy compounds. Neither 4-DMM nor NA-4-DMM, however, are known in mammalian tissues and no metabolic route for their formation has been established in mammals. 10 references.

118402 Gorodetzky, Charles. NIMH Addiction Research Center, P.O.Box 2000, Lexington, KY Sensitivity of thin-layer chromatography for detection of 16 opioids, cocaine and quinine. (Unpublished paper). Lexington, KY, NIMH, 1972, 12 p.

A method developed to quantitatively evaluate the sensitivity of thin layer chromatography (TLC) for detection of 16 opioids, cocaine and quinine is presented. For each drug studied, seven different amounts of the drug and a solvent control were randomly spotted across a 20 x 20 cm thin layer plate. For each amount of drug the ratio of the number of spots detected to the number of spots plated was determined, converted to a percentage, and plotted on log probability paper. Sensitivity data for 16 opioids, cocaine and quinine, using iodoplatinate alone and followed by ammoniacal silver nitrate and potassium permanganate for spot detection showed that TLC is not uniformly sensitive for the detection of all opioids. Adding silver nitrate and potassium permanganate after iodoplatinate produced an increase in sensitivity, with the exception of the arylpiperidines (levallorphan, propoxyphene, cocaine and quinine). A relative detection index for each drug, taking into account sensitivity for detection by TLC, euphorogenic dose, and 24 hour urinary excretion relative to morphine showed that all opioids would not be predicted to be equally detectable in the urine following administration of equieuphorogenic doses. Rf data showed widely overlapping tolerance limits between drugs, indicating that the Rf of a single unknown spot would be expected to be a poor measure of specificity under these TLC conditions. 26 references. (Author abstract)

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

108971 Lemke, Thomas L.; Hester, Jackson B.; Rudzik, Allan D. College of Pharmacy, University of Houston, Houston, Texas 77004 A new 2,6-difluorobenzodiazepinone. *Journal of Pharmaceutical Sciences.* 61(2):275-277, 1972.

The synthesis of 7-chloro-l,3-dihydro-5-c(2,6-difluorophenyl) 2H-l,4-benzodiazepin-2-one, a new 2,6-difluorobenzodiazepinone, is reported. The compound was tested in mice and found to be very potent when compared to chlordiazepoxide and diazepam, which are strong tranquilizers and muscle relaxants. 10 references. (Author abstract modified)

116581 Mallion, K.B.; Todd, A.H.; Turner, R.W.; Bainbridge, J.G.; Greenwood, D.T.; Madinaveitia, J.; Somerville, A.R.; Whittle, B.A. Imperial Chemical Industries, Pharmaceuticals Division, Alderly Park, Macclesfield, Cheshire SK 10 4TG, England 2-(2-ethoxyphenoxymethyl)tetrahydro-1,4-oxazine hydrochloride, a potential psychotropic agent. *Nature (London).* 238(5360):157-158, 1972.

The properties of 2-(2-ethoxyphenoxymethyl)tetrahydro-1,4-oxazine hydrochloride, a potential psychotropic agent, were investigated in mice and cats. In mice, the compound (ICI 58834) was shown to reverse and to prevent reserpine or tetrabenazine induced hypothermia and ptosis, and in these tests was equipotent with the tricyclic antidepressant drug, desmethylimipramine. Given intravenously to anaesthetized cats it potentiated the contractile response to the nictitating membrane to preganglionic electrical stimulation of the ascending sympathetic trunk and also those elicited by intravenous injections of noradrenaline or 5-hydroxytryptamine. In vitro, in small concentrations, it potentiated the action of noradrenaline on the isolated rat vas deferens, as does desmethylimipramine, but at greater concentrations ICI 58834 alone induced dose related contractions of this tissue. In this respect its action is reminiscent of that of amphetamine. ICI 58834 is a compound with novel profile of neuropharmacological activity, possessing features in common with both amphetamine and the central nervous system depressants. It seems worthy of study in a variety of psychiatric disorders in man. 10 references.

117613 Tomkiewicz, M. Dept.of Pharmacology, Univ.College, London, England Amylobarbitone abolishes social dominance hierarchies in laboratory rats. *British Journal of Pharmacology (London).* 44(2):351P, 1972.

A study to establish whether amylobarbitone can alter dominance hierarchies in rats competing for water is presented. Hierarchies were established in young male rats. Intraperitoneal injections of a moderate dose of amylobarbitone 20 min before the rats were given access to water, completely abolished the previously stable hierarchies, so that all the rats spent approximately the same amount of time drinking from the spout. The injections of amylobarbitone were continued for 14 days but no discernible dominance orders emerged. At the end of this period all rats were injected daily with saline instead of amylobarbitone and, after a further 14 days, the original hierarchies reemerged. It is suggested that fear or conflict play a major role in maintaining dominance order in rats. 5 references.

03 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

106972 Forrest, I.S.; Otis, L.S.; Serra, M.T.; Skinner, G.C. Department of Psychiatry, Stanford University School of Medicine, Palo Alto, California Passage of 3H-chlorpromazine and 3H-tetrahydrocannabinol into the hair (fur) of various mammals. (Unpublished paper). Rockville, Md.NIMH, 1972, 7 p.

In light of evidence that chlorpromazine metabolites have been found in the hair of patients and experimental animals receiving the drug, tests were carried out with different species of mammals that took tracer doses of chlorpromazine tritiated at position 9 of the nucleus and with delta-9-tetrahydrocannabinol (THC) tritiated at positions 2, 4, 8, and 9 of the nucleus. Although none of the animals was followed until radioactivity was close to background, the values obtained as a meassure of the metabolite incorporated in their fur were of low percentage in all cases. Chlorpromazine administered to rodents and delta-9-THC administered to primates were incorporated into the fur at identical rates ranging from 0.3to 1.2%. This auxiliary route of drug detoxification appears to be a minor one. 7 references.

106975 Kazic, Tomislav; Kopin, Irwin J. Laboratory of Clinical Science, NIMH, Building 10, Room 2D-46, Bethesda, Maryland 20014 Effect of L-Dopa on physostigmine-induced hypertension in the rat. (Unpublished paper). Bethesda, Md.NIMH, 1972.

In a study of the effect of L-Dopa on hypertension induced by physostigmine in rats, potentiation was prevented by a peripheral decarboxylase inhibitor, MK-486 (L-alpha-(3,4-dihydroxybenzyl)-alpha-hydrazinopropionic acid monohydrate) administered in intravenous doses of 10 to 20mg/kg and was presumably a consequence of enhanced catecholamine release. When L-Dopa doses were increased to 50mg/kg intravenously and physostigmine was injected 3 min afterwards, the hypertensive response was diminished. Pretreatment with MK-486 prevented the inhibition by L-Dopa of the blood pressure response to physostigmine. The obtained results suggest that dopamine accumulation in the peripheral sympathetic neurons is responsible for the inhibition of blood pressure elevation by physostigmine and that L-Dopa or dopamine does not alter the centrally medicated sympathetic activation produced by the cholinesterase inhibitor. (Author abstract modified)

106976 Hawkins, R.A.; Biebuyck, J.F. St.Elizabeths Hospital, William A.White Building, Room 3, Washington, D.C. 20032 The effects of anaesthetic agents on brain tissue metabolite concentrations. (Unpublished paper). Washington, D.C.NIMH, 1972, 1 p.

Halothane, pentobarbitone sodium, and ketamine hydrochloride were administered to fed and 48 hour starved adult rats, after which the brains were removed instantly and frozen by a technique which permits a rapid stoppage of less than 1 sec of metabolic processes. Concentrations of intermediates of the glycolytic pathway and the tricarboxylic acid cycle were measured as well as those of the adenosine nucleotides, glutamate and glutamine. Halothane and pentobarbitone caused decreases of between 20 and 50% in the concentrations of 3-phosphoglycerate, lactate, pyruvate, and alpha-ketoglutarate, and an increase of 20 to 100% in glucose concentration. Adenosinetriphosphate concentrations were raised by 10% and those of adenosinediphosphate and adenosinemonophosphate were lowered by 10 to 20%. Ketamine had no significant effect on the concentrations of these intermediates except that of alpha ketoglutarate, which was raised by 20%.

All 3 agents caused a significant rise in tissue glutamine concentration. No changes in cerebral metabolite concentrations were found in brain tissue obtained 15 and 60 sec following intravenous injection of pentobarbitone at a stage when the rats were fully anesthetized. (Author abstract modified)

106979 Jacobowitz, David M. Laboratory of Clinical Science, NIMH, Bethesda, Maryland 20014 Long term effects of 6-hydroxydopamine injected into newborn rats. (Unpublished paper). Bethesda, Md.NIMH, 1972, 1 p.

Newborn rats were injected with 6-hydroxydopamine (6-OHDA) in daily doses of 50mg/kg intraperitoneally for 7 days and were sacrificed with control rats ranging in age from 1 month to 1 year in order to analyze norepinephrine concentration of the ventricle submaxillary gland, spleen, and brain. There was a 60 to 90% decrease in norepinephrine in all the organs studied over the entire period except in the brain, where levels remained unchanged. Injection of 6-OHDA into newborn rats was found to result in a reduced number of adrenergic nerves within most of the studied peripheral organs but did not cause an irreversible total sympathectomy. It appears that regrowth of nerve processes takes place more readily in sites within the organs where nerves were present at the time of birth, such as blood vessels. This fact may account for differences in adrenergic reinnervation. (Author abstract modified)

106980 Oliver, A.P.; Sims, K.; Bloom, F.E. Laboratory of Neuropharmacology, NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Response of cranial nerve nuclei to extracellular application of norepinephrine, serotonin and gamma-aminobutyrate. (Unpublished paper). Washington, D.C.NIMH, 1972.

Pharmacologic effects of norepinephrine, serotonin, and gamma-aminobutyrate were tested locally on identifiable neurons of specific afferent and efferent cranial nerve nuclei. The ventral brain stem surface was exposed in albino rats weighing 200 to 300 gm that were anesthetized with halothane. Cranial nerve trunks were dissected for stimulation during recording. Neurons were recorded extracellularly, and drugs were applied using the 5 barrel microiontophoresis technique. Recording sites were also identified by histologic examination. In all 38 neurons tested, norepinephrine caused a marked reduction in spontaneous firing. In all 8 synaptically driven cells, firing rate was reduced by norepinephrine to the same extent. Twenty two of the 38 cells were tested with serotonin; 18 were inhibited, and 4 were unaffected. All 19 neurons tested with gamma-aminobutyrate were inhibited. None of the cells tested was excited by application of these substances. (Author abstract modified)

106981 Weight, Forrest F.; Padjen, Ante. Laboratory of Neuropharmacology, NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Slow postsynaptic inhibition and sodium inactivation in frog sympathetic ganglion cells. (Unpublished paper). Washington, D.C. NIMH, 1972, 1 p.

The mechanism of generation of the slow inhibitory postsynaptic potential (slow IPSP) was investigated by intracellular registration of the bullfrog 10th lumbar sympathetic ganglion in type C ganglion cells in vitro. In the presence of nicotine, slow synaptic inhibition was generated in C cells by repetitive orthodromic C fiber (8th nerve) stimulation at a frequency of 50 per second for 2 to 5 sec. Membrane resistance, measured by a constant current pulse, increased markedly during the slow IPSP with a time course similar to the IPSP. Electrical hyperpolarization of the membrane increased the amplitude of the slow IPSP, whereas progressive depolarization decreased the amplitude of the IPSP and could reverse it to a depolarizing potential. The reversal potential of the slow IPSP was in the region of the sodium equilibrium potential, judged by abolition of the antidromic spike. Acetylcholine administered directly to the cell by iontophoresis produced effects identical to the slow IPSP. Removal of extracellular sodium ion abolished the slow acetylcholine inhibitory potential. The results can be explained by the hypothesis that the slow IPSP in frog sympathetic ganglion cells is mediated by acetylcholine and is generated by an inactivation of resting sodium conductance. (Author abstract modified)

107571 Sims, K.L.; Davis, G.A.; Bloom, F.E. Laboratory of Neuropharmacology, NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Rat brain L-3,4-dihydroxyphenylalanine decarboxylase and 5-hydroxytryptophan decarboxylase activities: subcellular and regional distribution. (Unpublished paper). Washington, D.C.NIMH, 1972, 20 p.

The subcellular and gross regional distribution in rat brain of L-3,4-dihydroxyphenylalanine decarboxylase and 5-hydroxytryptophan decarboxylase is described. Brain 3,4-dihydroxyphenylalanine decarboxylase activity in subcellular fractions is associated predominately with soluble fractions and its distribution in the various fractions closely parallels that of lactic acid dehydrogenase. Brain 5-hydroxytryptophan decarboxylase activity, unlike that of lactic acid dehydrogenase, is divided almost equally between soluble and particulate fractions, and its distribution within the particulate fractions is different from that of succinic acid dehydrogenase. Brain 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan decarboxylases exhibit a 7 fold divergence in relative specific activity when their respective distributions in subcellular fractions are compared. Similarly, the regional distributions of the 2 activities in rat brain do not parallel one another: there is a 4 fold difference when the ratio of the 2 activities in cerebellum is compared with the ratio found in striatum. 26 references. (Author abstract modified)

107600 Cheney, D.L.; Hanin, I.; Massarelli, R.; Trabucchi, M.; Costa, E. Preclinical Pharmacology Lab., NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Differential effect of vinblastine (Vb) on cholinergic and adrenergic neurons. (Unpublished paper). Washington, D.C.NIMH, 1972.

Male rats were killed 2 and 12 hours, 1, 2, 5, and 14 days after vinblastine (Vb) sulfate (3mg/kg, i.v.)administration. Norepinephrine (NE) levels decreased by 90%in heart and by 70% in salivary gland by 5 days followed by partial recovery within 14 days. In telencephalon and brain stem no effect was seen throughout the 14 day time period. Acetylcholine (ACh) levels, on the other hand, were normal during the 14 day time span in heart, salivary gland, superior cervical ganglion, telencephalon, and brain stem. Because anatomically the adrenal gland has no adrenergic axons and is innervated by cholinergic neurons, the effect of Vb was investigated 5 days following injection on ACh and NE levels in this organ. A 50%increase in adrenal cortex weight and a 125% increase in adrenal medulla weight was observed in Vb treated rats. However, levels of NE and ACh, when expressed per gland, did not change. The increase in weight was not affected by unilateral splanchnicectomy indicating that this increase is not transsynaptically mediated. From these data it is tentatively proposed that: 1) Vb or an active metabolite does not appear to cross the blood brain barrier; 2) since Vb is known to act on microtubules to inhibit axonal flow, microtubular proteins in cholinergic and adrenergic neurons might be different. (Author abstract)

107757 Molinoff, P.B.; Axelrod, J. Dept.of Biophysics, University College London, Gower St., London W.C.1, England Distribution and turnover of octopamine in tissues. *Journal of Neurochemistry.* 19(1):157-163, 1972.

Observations of occurrence and distribution of octopamine in animal tissues are reported. Enzymic assay demonstrated that it is a naturally occurring amine in a wide variety of animal species ranging from crustacea to mammals. Particularly high concentrations were found in the crustacean central nerve cord. In the rat it was shown to be localized to sympathetic nerve endings, have a subcellular distribution similar to that of norepinephrine, and be asymetrically distributed in the central nervous system. Turnover rate in heart was about 6 times that of norepinephrine. The physiological role of octopamine has not been established but it appears likely that it is a cotransmitter together with norepinephrine in the peripheral sympathetic nervous system. 21 references. (Author abstract modified)

107758 Reis, D.J.; Molinoff, P.B. Dept.of Neurology, Cornell University Medical College, Ithaca, New York 10021 Brain dopamine-beta-hydroxylase: regional distribution and effects of lesions and 6-hydroxy-dopamine on activity. *Journal of Neurochemistry.* 19(1):195-204, 1972.

A modification of a specific and sensitive radioassay was used to measure dopamine-beta-hydroxylase (DBH) in various regions of the rat central nervous system (CNS). Highest activity was found in the hypothalamus. Relative to activity in the hypothalamus activity in brainstem was 80%, in sensory motor cortex, 55%, in caudate nucleus 32%, and in cervical spinal cord 30%. Two to 3 weeks after a unilateral electrolytic lesion of the lateral hypothalamus, activity of DBH in the ipsilateral cerebral cortex fell to 17% of control values without changes in activity ipsi- or contralaterally in the brainstem. Thalamic lesions did not affect DBH activity. In cerebral cortex contralateral to the hypothalamic lesion, enzymic activity rose 30%. After intracisternal administra-

tion of 6-hydroxy-dopamine (6-OH-DA), cortical DBH activity fell to 20% of control values. Reserpine (3mg/kg subcutaneously for 3 days) did not increase the activity of DBH in brain regions but did increase the activity of DBH in adrenal gland 200%. Results suggest that: DBH is widely distributed in neurons in CNS with a regional pattern of activities that appears to parallel the levels of norepinephrine; DBH activity in the cerebral cortex depends on the integrity of structures (medial forebrain bundle) in lateral hypothalamus; DBH in brain areas lacking cell bodies of norepinephrine neurons (cerebral cortex) is contained in norepinephrine containing axon terminals and the activity of DBH in brain is not increased by reserpine under conditions that provoke marked increase of DBH activity in the adrenal gland. 37 references. (Author abstract modified)

108081 Nicoll, Roger A. Laboratory of Neuropharmacology, NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 The action of anesthetics on synaptic excitation and inhibition in the olfactory bulb. (Unpublished paper). Washington, D.C. NIMH, 1972.

The dendrodendritic inhibitory pathway in the olfactory bulb provides an ideal model for studying the effect of drugs on synaptic excitation and inhibition. Physiological studies on the extracellular field potentials have provided strong evidence that antidromic impulses in mitral cell dendrites synaptically depolarize granule cell processes and that these in turn synaptically inhibit the mitral cell dendrites. Pharmacological studies suggest that GABA is the transmitter mediating the granule cell inhibition. The action of a variety of anesthetics, on these synaptic events has been analyzed. Relatively large doses of anesthetics (40-70)mg/kg hexobarbital) reduced both the antidromic invasion of mitral cells and the synaptic excitation of granule cells, the latter being somewhat more sensitive to the anesthetics. A wide dose range of anesthetics (3-60mg/kg hexobarbital) prolonged the granule cell inhibition of mitral cells. The prolongation appeared to be a specific effect on the inhibitory synapse, in that it occurred at doses which had no effect on mitral cell antidromic invasion or on the synaptic excitation of granule cells. These results are compared to the action of anesthetics on other GABA mediated inhibitory pathways. Possible mechanisms by which anesthetics could specifically prolong synaptic inhibition are discussed. (Author abstract)

108113 Pincus, Jonathan H. Section of Neurology, Yale Univ.School of Medicine, New Haven, Conn. 06510 Diphenylhydantoin and ion flux in lobster nerve. *Archives of Neurology*. 26(1):4-10, 1972.

Diphenylhydantoin has been shown to have no effect on the rate of sodium efflux in resting or stimulated lobster nerves. The drug reduces sodium influx in stimulated nerves by 40% but has no effect upon sodium influx in resting nerves. These results are consistent with the view that the drug acts primarily by limiting the increase in sodium permeability which occurs during stimulation; they are inconsistent with the theory that the drug acts by stimulating the sodium - potassium pump. A review of some of the chemical and physiological data concerning the effects of diphenylhydantoin on a variety of tissues supports this hypothesis. 14 references. (Author abstract)

108114 Hadfield, M.Gary. Div.of Neuropathology, Medical College of Virginia, Box 17, Health Sciences Center, Richmond, Va. 23219 Uptake and binding of catecholamines: effect of diphenylhydantoin and a new mechanism of action. *Archives of Neurology*. 26(1):78-84, 1972.

Diphenylhydantoin altered the uptake and binding of catecholamines in rat brain. In synaptosomes, uptake of radioactively labeled norepinephrine was stimulated under anoxic conditions while uptake was inhibited under more physiologic conditions. In intact brain slices uptake of dopamine labeled with tritiated water was inhibited in caudate - putamen and stimulated in hypothalamus. Subcellular distribution studies of diphenylhydantoin labeled with carbon 14 showed differential binding of the drug to several subcellular fractions. The binding of diphenylhydantoin sodium to microsomes and synaptosomes may alter the synthesis or activity of ATPase, an enzyme controlling neurotransmitter uptake and binding. Suggestions for future research are included. 20 references. (Author abstract modified)

108446 Downing, O.A. Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, England Effect of amphetamine on the transmission of repetitive impulses through the isolated superior cervical ganglion of the rat. *British Journal of Pharmacology (London)*. 44(1):71-79, 1972.

The cervical sympathetic trunk of the isolated rat superior cervical ganglion was stimulated with short bursts of repetitive pulses. At room temperature with rates of stimulation of 4 Hz and

above, the ganglionic action potentials were reduced in size. Amphetamine, which caused some depression of transmission during stimulation at 0.1Hz, caused a partial reversal of the depression of transmission occurring with rates of stimulation above 4 Hz. This action of amphetamine was mimicked by adrenaline and noradrenaline but not by isoprenaline and was unaffected by propranolol but was abolished by prior application phenoxybenzamine. Furthermore, this action of amphetamine was unaltered in ganglia taken from rats pretreated with reserpine (single dose of 6mg/kg, 16 h before dissection). Amphetamine had no effect on the surface potentials of the ganglion or on changes in these potentials produced by concentrations of carbachol. Amphetamine has a direct action on alpha-adrenoceptors situated at presynaptic sites. 18 references. (Author abstract)

108447 Yamaguchi, T. Department of Physiology, Faculty of Medicine, Kyushu University, Fukuoka, Japan Effects of 5-hydroxytryptamine on isolated strips of the guinea-pig stomach. ***British Journal of Pharmacology (London).*** **44(1):100-108, 1972.**

The effects of 5-hydroxytryptamine (5-HT) on isolated strips of the longitudinal and circular muscles of the guinea pig stomach were investigated. 5-HT (0.1-1 microgram/ml) increased the resting tension of the longitudinal muscle while it decreased that of the circular muscle. These effects were blocked by lysergic acid diethylamide (LSD), but were not affected by tetrodotoxin, hyoscine or morphine. Electrical stimulation caused contraction in the longitudinal muscle, and contraction followed by relaxation in the circular muscle. In both the longitudinal and circular muscles, the evoked contractions were potentiated by 5-HT. This effect was blocked by tetrodotoxin, hyoscine and morphine, but was not affected by LSD. In the stomach as well as the intestine of the guinea pig, there are 2 kinds of 5-HT receptors: the morphine sensitive M-receptor is situated on the intramural nerves and the D-receptor on the smooth muscle cells. 10 references. (Author abstract modified)

108448 Clark, B.; Thompson, J.W. Department of Biochemistry, Research and Development Laboratories, Fisons Ltd., Pharmaceutical Division, Loughborough, Leeds, England Analysis of the inhibition of pethidine-N-demethylation by monoamine oxidase inhibitors and some other drugs with special reference interactions in man. ***British Journal of Pharmacology (London).*** **44(1):89-99, 1972.**

N-Demethylation of pethidine was studied in microsomal suspensions from unstarved male rat liver and the N-demethylase identified as belonging to the class of hepatic microsomal mixed function oxidases. A study of the structure/action relationships of compounds inhibiting pethidine N-demethylase revealed that hydrazine derivatives, including phenylhydrazine, methylphenylhydrazine, and mebanazine, were all potent competitive inhibitors. Pethidine N-demethylase was only slightly inhibited by histamine and amphetamine but not by adrenaline and ephedrine nor by several miscellaneous compounds including piperidine, N-ethylpiperidine, N-methylpiperidine, N-methylammonium, hydrallazine, or pethidinic acid. Several psychotropic drugs were all found to be potent competitive inhibitors of pethidine N-demethylase. These included monoaminoxidase inhibitors. These results are discussed in relation to the clinically observed drug interactions which may occur between monoamine oxidase inhibitors and pethidine. Since many different groups of drugs, including monoamine oxidase inhibitors, tranquilizers, tricyclic antidepressants, steroids, nalorphine, SKF 525A and barbiturates compete for cytochrome P450 reductase, it is possible that this mechanism may account, at least in part, for the observed interactions of these various drugs in man. 48 references. (Author abstract modified)

108623 Mussini, E.; Marcucci, F.; Fanelli, R.; Guaitani, A.; Garattini, S. Istituto di Ricerche, Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy Analytical and pharmacokinetic studies on the optic isomers of oxazepam succinate half-ester. ***Biochemical Pharmacology (Oxford).*** **21(1):127-129, 1972.**

The toxic and anticonvulsant effects of the 2 optic isomers of oxazepam succinate half-ester were studied in rats and mice. In addition, the blood levels of oxazepam obtained after the administration of the 2 isomers or the racemic form of oxazepam succinate half-ester were determined. The 2 isomers exerted different anticonvulsant activity when given 30 min.before metrazol: the ED50 of the (l) form was 3 times higher than that of the (d) form; the racemic form had an intermediate value. The LD50 of all forms is comparable. After intravenous administration,

the (d) isomer, the most powerful anticonvulsant form, led to the formation of higher or longer lasting levels of blood oxazepam than the (l) form in both mice and rats. Oxazepam formed from the succinate half-ester, independently from the isomeric form, shows a longer plasma half-life in mice than in rats. The difference between the 2 isomeric forms is not present when the oxazepam succinate half-esters are given by oral route to mice or to rats even if the animals were pretreated for 6 days with neomycin (1.5g/kg) by oral route to minimize a possible hydrolytic activity of the intestinal flora. The fact that there is a correlation between the anticonvulsant activity and the blood levels of oxazepam suggests that the succinate half-esters of oxazepam act by making available oxazepam. 5 references.

108624 Baldessarini, Ross J.; Lipinski, Joseph F.; Chace, Kenneth V. Department of Psychiatry, Massachusetts General Hospital, Boston, Mass. Effects of amantadine hydrochloride on catecholamine metabolism in the brain of the rat. ***Biochemical Pharmacology (Oxford).*** **21(1):77-87, 1972.**

The effects of the cyclic amine, amantadine hydrochloride, on the metabolism of catecholamines were investigated in rats. Large doses of the drug had minimal effects on cardiac norepinephrine stores, but produced small decreases in concentrations of norepinephrine in the brain, while having less effect on dopamine and no effect on serotonin. The drug altered the metabolism of previously intrathecally administered (3H)norepinephrine: there were small decreases of (3H)norepinephrine, but clear decreases of (3H)deaminated catechol metabolites and marked increases of (3H)normetanephrine for 1-6 hr, at times paralleling decreases in endogenous norepinephrine levels. Later, smaller increases of (3H)deaminated-O-methylated products appeared. These metabolic changes were not due to inhibition of monoamine oxidase by this drug. Amantadine decreased the retention by isolated nerve endings in vitro of previously intrathecally injected (3H)norepinephrine by a very small amount and competitively inhibited the initial uptake of (3H)d,l-norepinephrine by nerve endings of whole brain. This inhibition of uptake was somewhat greater in the cerebral cortex than in the corpus striatum. There was much less inhibition of the uptake of (3H)dopamine in both regions. Thus, part of the action of this drug in Parkinson's disease may be due to inhibition of uptake and retention of catecholamines at central nerve terminals. However, since the doses required to produce changes in vivo were much higher than those used clinically, these findings may reflect nonspecific or toxic effects of the drug. 31 references. (Author abstract modified)

108787 Kaplan, E.R.; Sapeika, N.; Zwarenstein, H. Dept.of Pharmacology, Univ.of Cape Town, Cape Town, South Africa Effect of fenfluramine, dexamphetamine and diethylpropion on phosphoglucomutase, 3-phosphoglycerate kinase and pyruvate kinase of mouse muscle. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(1):47-50, 1972.**

The effect of Fenfluramine hydrochloride and dexamphetamine sulfate on 3-phosphoglycerate kinase and pyruvate kinase in homogenates of mouse muscle was studied. The effect of diethylpropion hydrochloride on these enzymes and on phosphoglucomutase was also investigated. Fenfluramine and dexamphetamine inhibit pyruvate kinase but have no action on 3-phosphoglycerate kinase whereas EDTA inhibits both these enzymes. Diethylpropion has no action on phosphoglucomutase and 3-phosphoglycerate kinase, and only a slight action on pyruvate kinase. 3 references. (Author abstract modified)

108817 Galzigna, L. Department of Biological Chemistry, University of Padova, 35100 Padova, Italy Interaction of chlorpromazine with adrenochrome and interference of a possible endogenous psychotogenic agent with some synaptic enzyme activities. ***Biochemical Pharmacology (Oxford).*** **21(2):203-207, 1972.**

The mode of action of chlorpromazine and the action of the acetylcholine - adrenochrome complex on some synaptic enzyme activities were investigated. Chloropromazine is able to interact with adrenochrome yielding a complex more stable than the acetylcholine - adrenochrome complex postulated as the endogenous psychotogenic agent in mental illness. The toxicity of the acetylcholine - adrenochrome complex is related to its ability of inhibiting acetylcholinesterase and activating monoaminoxidase obtained from extracts of baboon brain. 16 references. (Author abstract modified)

108818 Pal, B.; Ghosh, J.J. Department of Biochemistry, University College of Science, Calcutta University, Calcutta 19, India 1-delta9-

tetrahydrocannabinol --effects on the urinary excretion of 5-hydroxyindole acetic acid. ***Biochemical Pharmacology (Oxford).*** **21(2):263-264, 1972.**

In an attempt to understand further the effects of delta9-tetrahydrocannabinol delta9-THC on the metabolism of 5-hydroxytryptamine (5-HT), the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) was studied in rats. The 5HIAA content in the urine was elevated by delta9-THC. A slight increase was observed following a single injection at 10 mg/kg; treatment for 7 consecutive days at the same dose level caused a moderate increase. This latter rise was less marked than that due to a single massive dose of the drug (100mg/kg). Since the excretion of creatinine did not significantly change in all experiments after delta9-THC, the glomerular filtration was not affected by the drug and therefore, any change in the 5-HIAA excretion due to the cannabinol may be assumed to be absolute. 11 references.

108972 Felmeister, Alvin. College of Pharmacy, Rutgers University, New Brunswick, N.J. 08903 Relationships between surface activity and biological activity of drugs. ***Journal of Pharmaceutical Sciences.*** **61(2):151-164, 1972.**

A review of studies of the relationships between surface activity and biological activity of drugs is presented. Included are: local anesthetics, psychotherapeutic and sedative - hypnotic agents, antibiotics and antibacterial agents, gaseous agents, hormones, fat soluble vitamins, chemical carcinogens, acetycholine, antihistamines, and surface active agents. Studies of the interaction of drug and other agents at the air/water or monolayer/water interface have provided data that contribute to a better understanding of the site of action and mechanism of interaction of such components at biological membranes. In many instances, a remarkable correlation between surface activity and biological function was observed. Furthermore, investigations of the interaction of physiologically important endogenous materials with monolayers of lipids and proteins have provided information on the biological function of these materials. 15 references.

108993 Herrera, Francisco C. Departamento de Ecologia, Instituto Venezolano de Investigaciones Cientificas, Caracas, Venezuela Inhibition of lithium transport across toad bladder by amiloride. ***American Journal of Physiology.*** **222(2):499-502, 1972.**

Amiloride blocks sodium penetration across the urinary surface of bladder epithelium. In bladders exposed to lithium Ringer on the mucosal side and choline Ringer on the serosal side, short circuit current, potential difference, and net mucosal to serosal lithium transport were much lower in bladders exposed to amiloride than in controls. Amiloride decreased tissue lithium accumulation. Losses of tissue potassium and sodium toward the serosal solution were lower, and tissue potassium was higher in amiloride treated bladders than in controls. Losses of tissue potassium and sodium toward the mucosal solution were unaffected by amiloride. The effect of amiloride on lithium movement appears to be similar to that on sodium transport: it blocks the entry of lithium across the urinary epithelial surface. This determines a fall of the intraepithelial lithium which is moving across the bladder and brings about a fall in transbladder lithium flux, potential difference, and short circuit current. Thus, lithium and sodium fluxes across the apical epithelial surface appear to involve sites sensitive to the same agent, amiloride. 18 references. (Author abstract)

109038 Harris, Ruth. Maudsley Hospital, Denmark Hill, London S.E.5, England The EEG in anaesthetized juvenile baboons. ***Electroencephalography and Clinical Neurophysiology (Amsterdam).*** **32(1):81-83, 1972.**

One hundred and twenty four EEGs were obtained from juvenile baboons during anesthesia with phencyclidine hydrochloride (Sernyl) and pentobarbitone (Nembutal). Changing EEG patterns were found which could be related to the time interval from the onset of anesthesia. It was found, with some variations in individual animals, that a relatively stable EEG was seen from 15 to 45 min after starting anesthesia. It is suggested that evaluation of these variations are important in experiments where the EEG is being used to monitor changes in cerebral function. 7 references. (Author abstract)

111217 Schechter, Paul J.; Lovenberg, Walter; Sjoerdsma, Albert. Experimental Therapeutics Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, Md. 20014 Dissociation of morphine tolerance and dependence from brain serotonin synthesis rate in mice. ***Biochemical Pharmacology (Oxford).*** **21(5):751-753, 1972.**

The activity of tryptophan hydroxylase in whole brains of morphine tolerant and control mice was studied. There was no difference in enzyme activity between the 2 groups. The concentration of serotonin in whole brains of placebo implanted and morphine tablet implanted mice at various times after monoamine oxidase inhibition was determined. No significant differences were found in whole brain serotonin levels between control and morphine injected animals at 0, 30, 60, and 120 min. after pargyline administration. These findings are in contrast to previous reports. Species differences and hypotheses are discussed. It is felt that a mechanism other than one involving brain indoles should be sought to explain the tolerance phenomenon. 23 references.

111220 Colburn, Robert W.; Kopin, Irwin J. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Md. 20014 Effects of reserpine and tyramine on release of norepinephrine from synaptosomes. ***Biochemical Pharmacology (Oxford).*** **21(5):733-736, 1972.**

Synaptosomes incubated with norepinephrine-14C and subsequently treated with reserpine released labeled deaminated products of the catecholamine. Tyramine, however, resulted in release of unmetabolized norepinephrine-14C. These findings are similar to those found in peripheral organs and suggest that in brain, as well as in peripheral sympathetic nerves, intraneuronal release of norepinephrine is attended by deamination. 11 references. (Author abstract)

111300 Quastel, D.M.J.; Hackett, J.T.; Okamoto, K. Department of Pharmacology, University of British Columbia, Vancouver, British Columbia Presynaptic action of central depressant drugs: inhibition of depolarization-secretion coupling. ***Canadian Journal of Physiology and Pharmacology (Ottawa).*** **50(3):279-284, 1972.**

Central depressant drugs probably inhibit the mechanism by which transmitter secretion is coupled to nerve terminal depolorization, perhaps by suppression of a depolorization sensitive calcium - permeability system. Chlorpromazine, like raised osmotic pressure, not only increased spontaneous miniature endplate potential frequency (F) in mouse diaphragm (in vitro) but also depressed the slope of log F versus focal presynaptic depolarization. It also depressed the slope of log F versus calcium concentration in raised potissium ion solution (constant depolarization). Similar effects were seen with pentobarbital, chloral hydrate, chloroform, and lowered pH. The drugs have similar actions in locust muscle, where the transmitter is not acetylcholine. 12 references. (Author abstract modified)

111511 Murphey, D.L.; Dill, R.E. Dept.of Microscopic Anatomy, Baylor College of Dentistry, Dallas, Texas 75226 Chemical stimulation of discrete brain loci as a method of producing dyskinesia models in primates. ***Experimental Neurology.*** **34(2):244-254, 1972.**

The technique of chemical stimulation of the CNS was utilized in a study designed to develop models of dyskinesias in a primate. Four sites in the extrapyramidal motor system of squirrel monkeys were stimulated with carbachol, a cholinergic drug. This was achieved by intracranial injection of microgram amounts of the drug via chronically implanted cannulae. Injection of carbachol into the neostriatum, both caudate nucleus and putamen, produced a hyperkinetic choreiform syndrome. Tremor and chorea in the contralateral limbs and facial dyskinesia with sialorrhea were the most common results of this procedure. Carbachol stimulation of the medial globus pallidus produced an akinetic hyperextension syndrome characterized by an immobile extension of the contralateral limbs. The extended limbs had the appearance of being rigid. Brief bursts of tremor or chorea were rarely superimposed. Carbachol stimulation of the subthalamus produced a hyperactive state consisting of ceaseless ambulation, climbing, and circling. All of the above effects were reproducible and consistent for each cannula site, suggesting that specific dyskinesias can be elicited by cholinergic stimulation of discrete loci in the extrapyramidal system. Such information is critical to the understanding of the physiology of these structures. 26 references. (Author abstract)

111595 Palfreyman, M.G.; Leonard, B.E. Beechams Research Laboratories, the Pinnacles, Harlow, Essex, England Some neurochemical correlates of convulsive activity in the rat brain. ***Biochemical Pharmacology (Oxford).*** **21(3):355-362, 1972.**

The effects of seizures induced by leptazol, electroshock and high intensity sound were studied on some parameters of glycolysis in the rat brain. Whereas the glycolytic flux was increased to approximately the same extent irrespective of the means by which the seizure was induced, lep-

tazol produced a biphasic change in total brain hexokinase activity. The activity of this enzyme was increased during the initial stages of the seizure, but decreased with increasing seizure severity. The possible reasons for the effects are discussed. 28 references. (Author abstract)

111596 Papapetrou, P.D.; Marchant, B.; Gavras, H.; Alexander, W.D. University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, U.K. Biliary excretion of 35S-labelled propylthiouracil, methimazole and carbimazole in untreated and pentobarbitone pretreated rats. *Biochemical Pharmacology (Oxford).* 21(3):363-377, 1972.

The excretion of 35S-labelled antithyroid drugs 4(6)-propyl-2-thiouracil (PTU), methimazole and carbimazole in the bile of the rat was studied. Carbimazole had the highest biliary clearance and PTU the lowest. The nature of the 35 S-compounds excreted in the bile was investigated using thin-layer chromatography. About 10.6% of 35S-radioactivity in the bile of rats injected with methimazole was due to free methimazole; about the same percentage of free methimazole was observed after carbimazole injection. There was no free carbimazole detectable in the bile. These findings suggest that carbimazole is metabolized through methimazole. None of the metabolites of the 3 drugs which appeared in the bile had R(f) similar to free thiourea or to conjugates of thiourea appearing in the bile of rats injected with (35S)thiourea. It was concluded that hepatic metabolism of the 3 drugs does not occur through thiourea. 14 references. (Author abstract modified)

111597 Dodge, Patrick W.; Takemori, A.E. Pharmacodynamics Department, Division of Experimental Pharmacology, Abbott Laboratories, North Chicago, Ill. 60064 Effects of morphine, nalorphine and pentobarbital alone and in combination on cerebral glycolytic substrates and cofactors of rats in vivo. *Biochemical Pharmacology (Oxford).* 21(3):287-294, 1972.

The effects of the administration of morphine, nalorphine and pentobarbital alone and in combination on glycolytic substrate and cofactor levels in rat brain were examined. Pentobarbital increased the concentrations of glucose and glucose 6-phosphate and produced a fall in pyruvate and lactate concentrations. Morphine also increased glucose and glucose 6-phosphate concentrations. Both pentobarbital and morphine produced increases in brain adenosine triphosphate and creatine -- phosphate concentrations, but only morphine reduced the concentration of adenosine monophosphate. Nalorphine had no effect on the levels of glycolytic intermediates when given alone, but reversed the changes brought about by morphine. Nalorphine did not reverse the changes produced by pentobarbital. The glycolytic substrate and cofactor levels in brains of chronically morphinized rats did not differ from those in animals that received saline solution over the same period. A challenge dose of 15mg/kg of morphine administered to the chronically morphinized rats revealed that a large degree of tolerance to the effects of morphine on glycolytic intermediates and cofactors can be demonstrated. The process of withdrawal produced by injections of nalorphine in the chronically morphinized rats did not appear to be related to changes in brain concentrations of glycolytic intermediates. 10 references. (Author abstract modified)

111823 Aghajanian, G.K. Yale University School of Medicine, New Haven, Connecticut Influence of drugs on the firing of serotonin-containing neurons in brain. *Federation Proceedings.* 31(1):91-96, 1972.

A new approach to the study of drug effects on brain serotonin involves monitoring of the single unit activity of brainstem raphe neurons. Perikarya of neurons situated in the raphe nuclei of the brainstem have been shown by fluorescence histochemical methods to be the principal, if not the only, serotonin containing neurons in the brain. On the basis of this knowledge studies were carried out showing that various drugs believed to act via brain serotonin have marked effects on the rate of firing of raphe neurons. D-Lysergic acid diethylamide, which like serotonin contains an indole nucleus, was found to be a potent inhibitor of raphe unit firing. Both monoamine oxidase inhibitors and the initial serotonin precursor, L-tryptophan, increase brain serotonin content and raphe cell fluorescence. They both were found also to depress raphe firing, though not as rapidly or completely as in the case of D-lysergic acid diethylamide. Contrary to expectation p-chlorophenylalanine, an inhibitor of serotonin synthesis, did not prevent either the L-tryptophan-induced enhanced fluorescence or depression of raphe firing. This result suggests that indoleamines in addition to serotonin may be in-

volved in raphe cell function. In any case, the findings generally indicate a reciprocal relationship between firing rate and the levels of indoleamines within raphe neurons (firing rate decreases as indoleamine content increases). The effects of D-lysergic acid diethylamide would fit into such a scheme if it were assumed that this drug mimics the action of serotonin (or other indoleamines) at postsynaptic sites of the raphe neurons. 37 references. (Author abstract)

111826 Bloom, F.E.; Hoffer, B.J.; Siggins, G.R.; Barker, J.L.; Nicoll, R.A. Laboratory of Neuropharmacology, NIMH, St.Elizabeth's Hospital, Washington, D.C. Effects of serotonin on central neurons: microiontophoretic administration. ***Federation Proceedings.*** **31(1):97-106, 1972.**

Effects of serotonin on central neurons are discussed. Iontophoretic application of serotonin alters neuronal activity in every brain region in which it has been tested. Depending upon the region involved and the functional classification of the neuron tested the response can be either excitation or depression. Under a variety of experimental conditions that exclude presynaptic interneuronal sites, the action of serotonin on cerebellar Purkinje cells is solely depressant. However, cytochemical and ultrastructural observations suggest that granule cells are a more likely site for synaptic actions of serotonin and here the effect is excitation. Further histochemical and cytological confirmation is provided for a possible serotonin mediated synaptic connection to certain cells in the rat pontine raphe nuclei; these neurons had been shown to respond to electrical stimulation of a serotonin containing neuron population and to iontophoresis of serotonin by excitation. Neurons in the suprachiasmatic nucleus of the cat hypothalamus also receive a rich serotonin containing input; they respond to stimulation of the serotonin containing brain stem nuclei and to iontophoresis of serotonin by depression of activity. Further progress in the identification of serotonin as the transmitter for these synaptic sites requires the development of selective serotonin specific synergists and antagonists. 64 references. (Author abstract modified)

112026 Cohen, Gerald; Mytilineou, Catherine; Barrett, Robert E. Clinical Research Center for Parkinson's and Allied Diseases, Columbia University College of Physicians and Surgeons, N.Y. 6,7-Dihydroxytetrahydroisoquinoline: uptake and storage by peripheral sympathetic nerve of the rat. ***Science.*** **175(4027):1269-1272, 1972.**

6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline is a pharmacologically active alkaloid that can be formed by condensation of dopamine with formaldehyde. Fluorescence microscopy was used to study in vitro the uptake and storage of this compound by sympathetic nerves of the rat iris. Rats were treated with reserpine or with the methyl ester of alpha-methyl-p-tyrosine in order to deplete the endogenous catecholamine stores. Accumulation of the alkaloid was about 1/10 that of norepinephrine. Uptake was completely blocked by desmethylimipramine. These results offer some explanation for the sympathomimetric properties of the alkaloid. Similar results can be expected for similar tetrahydroisoquinolines that may be formed in vivo from endogenous catecholamines during ingestion of alcoholic beverages. 24 references. (Author abstract modified)

112067 Planz, Georg; Quiring, Klaus; Palm, Dieter. Pharmakologisches Institut der Universitat, Frankfurt am Main, West Germany Turnover rates of monoamine oxidases: recovery of the irreversibly inhibited enzyme activity and the influence of isoproterenol. ***Life Sciences.*** **11(3):147-160, 1972.**

The turnover rates of monoamine oxidases (MAO) can be determined by measuring the rates of recovery of the irreversibly inhibited enzyme. The rates obtained reflect de novo enzyme synthesis and follow first-order kinetics. The rates of recovery of irreversibly inhibited MAO were specific for monoamine oxidases in different tissues and independent of the irreversible inhibitor used. Similar rates were obtained when protein turnover was directly measured. In the submandibular glands of rats, isoproterenol enhanced both synthesis and turnover of MAO, whereas in the heart no effect of isoproterenol on MAO was seen. 22 references. (Author abstract modified)

112068 Clarke, D.E.; Smookler, H.H.; Hadinata, J.; Chi, C.; Barry, H., III. Department of Pharmacology, University of Pittsburgh, School of Pharmacy, Pittsburgh, Pennsylvania 15213 Acute effects of 6-hydroxydopa and its interaction with Dopa on brain amine levels. ***Life Sciences.*** **11(3):97-102, 1972.**

The intravenous administration of 400mg/kg of DL-6-hydroxydopa (6-OH-Dopa) to mice markedly depleted whole brain norepinephrine (NE).

Whole brain levels of dopamine (DA) were not affected, whereas 5-hydroxytryptamine (5-HT) levels were slightly elevated. These findings show that even after a high dose of 6-OH-Dopa only brain NE appears to be markedly affected. This action might be mediated indirectly, through the endogenous formation of 6-hydroxydopamine. DL-Dopa (Dopa), 400mg/kg given intraperitoneally, failed to alter the whole brain level of NE, but depleted brain 5-HT caused by Dopa were greatly potentiated by prior treatment with 6-OH-Dopa. Although the mechanism of this interaction is unknown, the enhanced effectiveness of Dopa following 6-OH-Dopa administration provides in vivo evidence that Dopa induced depletion of 5-HT may be mediated by endogenously formed DA. 12 references. (Author abstract)

112073 Yeh, S.Y.; Mitchell, C.L. NIMH Addiction Research Center, Lexington, Ky. 40507 Effect of monoamine oxidase inhibitors on formation of morphine glucuronide. ***Biochemical Pharmacology (Oxford).*** **21(4):571-578, 1972.**

The inhibition of the formation of morphine glucuronide in vitro by 5 monoamine oxidase inhibitors is described. Pargyline and phenelzine and tranylcypromine were competitive inhibitors of morphine glucuronidation, while isocarboxazide was a mixed type inhibitor. Nialamide, in the concentrations studied, did not significantly inhibit the formation of morphine glucuronide. 15 references. (Author abstract modified)w

112167 Adler-Graschinsky, Edda; Langer, S.Z.; Rubio, M.C. Paraguay 2155, 7 Piso, Buenos Aires, Argentina Metabolism of norepinephrine released by phenoxybenzamine in isolated guinea-pig atria. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(2):286-301, 1972.**

Phenoxybenzamine induced a slowly developing and concentration dependent positive chronotropic effect in isolated spontaneously beating guinea pig atria. The rate accelerating effect was blocked by propranolol or by reserpine pretreatment and, therefore, appears to be mediated through endogenous norepinephrine. Pargyline pretreatment increased the rate accelerating effects of phenoxybenzamine. Supersensitivity to norepinephrine was obtained in the presence of phenoxybenzamine except for the concentration of 10 micrograms/ml which induced a shift to the right and a depression of the maximum. The latter was related to the decelerating effects of large concentrations of phenoxybenzamine. In atria, in which the norepinephrine stores were labeled with 3H-norepinephrine, phenoxybenzamine (3 micrograms/ml) produced an increased release of 3H-norepinephrine and of 3H-34-dihydroxyphenylglycol (DOPEG). The metabolic pattern of transmitter released by phenoxybenzamine was similar to that obtained in the presence of a reserpine-like agent, Ro 4-1284. Inhibition of presynaptic monoamine oxidase with bretylium resulted in a selective decrease in the spontaneous outflow of the deaminated glycol, DOPEG. These results support the view that DOPEG is formed predominantly as a result of presynaptic monoamine oxidase activity. In the presence of cocaine, the small increase in spontaneous release of tritiated compounds was accounted for entirely norepinephrine. Phenoxybenzamine can be described as reserpine-like as far as the presynaptic metabolism of the released norepinephrine and as tyramine-like with regard to its ability to release the transmitter and to sensitize to norepinephrine. 27 references. (Author abstract)

112170 Romero, J.A.; Chalmers, J.P.; Cottman, K.; Lytle, L.D.; Wurtman, R.J. Massachusetts Institute of Technology, 56-245, Cambridge, Mass. 02139 Regional effects of L-dihydroxyphenylalanine (L-dopa) on norepinephrine metabolism in rat brain. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(2):277-285, 1972.**

After 10 daily doses of L-dihydroxphenylalanine (L-dopa) (100mg/kg i.p.), rats received intracisternal tritiated norepinephrine (3H-NE) and a final dose of L-dopa 5 minutes later. They were killed at intervals during the next 6 hours and their brains were dissected into 5 regions (striatum, hypothalamus, brainstem, telencephalon, and cerebellum) and assayed for NE, L-dopa, dopamine, 3H-NE and 3H-NE metabolites. L-Dopa caused decreases in the concentrations of O-methylated 3H-NE metabolites especially in the telencephalon, brain, and cerebellum. As long as L-dopa was detectable in the brain, total NE pools were generally enlarged in these regions, as were dopamine levels in both the striatum and the rest of the brain. 3H-NE, decline of 3H-NE specific activity and, calculated turnover rate. Generally, these 3 parameters of 3H-NE specific kinetics were accelerated initially and then decelerated as a result of L-dopa treatment, with regional differences in magnitude and

time course. In the hypothalamus, accelerated 3H-NE disappearance and turnover persisted throughout the period examined. 38 references. (Author abstract)

112171 Bhatnagar, R.K.; Moore, K.E. Department of Pharmacology, University of Iowa, Iowa City, Iowa Regulation of norepinephrine contents in neuronal cell bodies and terminals during and after cessation of preganglionic stimulation. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(2):265-276, 1972.**

The contents of norepinephrine (NE) in cell bodies (superior cervical ganglia) and terminals (submaxillary salivary glands) of postganglionic sympathetic neurons were determined in cats during, immediately after, and 2 and 6 hours after cessation of 3 hours of preganglionic electrical stimulation. In ganglia, neither the NE contents nor the rates of formation of NE-14C from tyrosine-14C or dopamine-14C were altered during the stimulation or poststimulation periods. Stimulation for 1 hour reduced the amount of NE in terminals to 40% of control; this reduced content was maintained when stimulation continued for 3 hours. The stimulus induced reduction of NE in terminals was enhanced if either synthesis or reuptake of NE was blocked by alpha-methyltyrosine or desmethylimipramine, respectively. During the poststimulation period the amount of NE in the terminals increased to 65% of control within 2 hours, and then remained at this reduced value during the next 4 hours. alpha-Methyltyrosine, but not desmethylimipramine, prevented this partial recovery of NE. The synthesis of NE-14C from tyrosine-14C increased during and immediately after cessation of stimulation, but 6 hours later the conversion of tyrosine-14C to NE-14C was the same in stimulated and nonstimulated terminals. The failure of NE to return to control values after stimulation was not the result of reduced activity or dopamine-beta-hydroxylase because 6 hours after cessation of stimulation the conversion of dopamine-14C to NE-14C was accelerated. Thus, recovery of NE stores in nerve terminals after depletion by preganglionic stimulation is effected by an increased rate of synthesis of this amine from tyrosine, probably involving release of feedback inhibition, and from dopamine, involving an unknown mechanism. 27 references. (Author abstract)

112444 Philips, David S.; Denney, Duane D.; Robertson, Richard T.; Hicks, Leslie H.; Thompson, Richard F. Departments of Medical Psychology and Psychiatry, University of Oregon Medical School, Portland, Oregon 97201 Cortical projections of ascending nonspecific systems. ***Physiology & Behavior.*** **8(2):269-277, 1972.**

Areal distributions on cerebral cortex of several types of nonspecific activity were compared in cat. Spontaneous spindle bursts in pentobarbital and cerveau isole preparations, nonspecific cortical association responses evoked by peripheral stimuli in the chloralosed animal, and short latency cortical responses evoked by single shock stimulation of the midbrain reticular formation were all found to have essentially identical cortical distributions. These occurred in 4 2 major foci, 2 on the middle suprasylvian gyrus, 1 on the anterior lateral gyrus, and one on pericruciate cortex surrounding the cruciate sulcus. 38 references. (Author abstract)

112721 Selye, Hans; Szabo, Sandor. Institut de medecine et de chirurgie experimentales, University of Montreal, Montreal, Quebec, Canada Effect of catatoxic steroids upon lidocaine intoxication. ***Conditional Reflex.*** **7(1):11-18, 1972.**

Observations are presented which show that certain catatoic steroids give almost complete protection against severe lidocaine intoxication in rats. None of the other steroids, nor thyroxine, phenobarbital, or diphenylhydantoin, shared this effect. Most of the prophylactic effects of catatoxic steroids have been traced to the induction of drug metabolizing hepatic microsomal enzymes. It is noteworthy, therefore, that phenobarbital and diphenylhydantoin, potent inducers of hepatic microsomal enzymes, were ineffective in protecting the rats against lidocaine. It must be assumed that either this particular protective action of catatoxic steroids does not depend upon such enzyme induction, or the enzyme activity induced by the steroids differs from that elicited by phenobarbital or diphenylhydantoin pretreatment. 14 references.

112969 Abbritti, Giuseppe; De Matteis, Francesco. Biochemical Mechanisms Section, Toxicology Unit, Medical Research Council, Carshalton, Surrey, England Decreased levels of cytochrome P-450 and catalase in hepatic porphyria caused by substituted acetamides and barbiturates. Importance of the allyl group in the molecule of the active drugs.

Chemico-Biological Interactions (Amsterdam). 4(4):281-286, 1972.

The effect of 4 substituted acetamides (2-allyl-2-isopropylacetamide; 2-propyl-2-isopropylacetamide; 2-phenyl-2-allylacetamide; and 2-phenyl-2,2-diethylacetamide) and of 2 barbiturates (diallylbarbituric acid and dipropylbarbituric acid) on the levels of cytochrome P-450 and catalase was studied and related to the induction of porphyria in the liver of rats. Drugs containing 1 or 2 allyl substituents were found to depress the activity of catalase and the levels of cytochrome P-450; they were also porphyrogenic. The significance of these findings is discussed in the light of recent evidence for destruction of liver heme in experimental porphyria. 12 references. (Author abstract modified)

113113 Wong, David T.; Van Frank, Richard M.; Horng, Jong-Sin; Fuller, Ray W. Eli Lilly Research Laboratories, Indianapolis, Indiana 46206 Accumulation of amphetamine and p-chloroamphetamine into synaptosomes of rat brain. ***Journal of Pharmacy and Pharmacology (London).*** **24(2):171-173, 1972.**

Observations on the localization of p-chloroamphetamine and amphetamine in subcellular particles of the rat brain are reported. Groups of four Sprague-Dawley rats (150-180g) were separately treated with equimolar doses of amphetamine (18mg/kg) and p-chloroamphetamine (24mg/kg). A crude mitochondrial preparation was obtained from a 30% brain homogenate, and a microsomal fraction was isolated. Most of the amphetamine (77%) was found in the post mitochondrial fraction; 62.5% of the amphetamine was associated with the high speed supernatant fraction. A total of 31.5% of the amphetamine was particle bound. The high speed supernatant fraction contained only 14.6% of p-chloroamphetamine, whereas the crude mitochondria and microsomes had 33% and 18.4% of the drug for a total of 51%that was particle bound. The synaptosomal fraction had the largest proportion of drug and myelin was next. p-Chloroamphetamine was associated with the synaptosomes but not the mitochondrial fraction. The association of p-chloroamphetamine with synaptosomes to a greater degree than occurred with amphetamine suggests a basis for differences in their pharmacological properties. 12 references.

113114 Cotillo, P.; Bonaccorsi, A. Programa de Farmacia y Bioquimica, Siron Puno 1002, Apartado 1760, Peru Observations on the interactions between desipramine and reserpine on adrenergic transmission in the rat. ***Journal of Pharmacy and Pharmacology (London).*** **24(2):103-107, 1972.**

The time course of the impairment of the adrenergic transmission induced by reserpine was examined on the inferior eyelid of rats pretreated with desipramine. Desipramine given before reserpine is able to counteract, in a dose dependent manner, the impairment induced in the first hours after reserpine. However, desipramine has only a limited effect, not dose dependent, when given after the reserpine treatment. 10 references. (Author abstract modified)

113116 Beckett, A.H.; Al-Sarraj, S. Dept.of Pharmacy, Chelsea College, University of London, Manresa Rd., London SW3, England The mechanism of oxidation of amphetamine enantiomorphs by liver microsomal preparations from different species. ***Journal of Pharmacy and Pharmacology (London).*** **24(2):174-176, 1972.**

The metabolism of d-amphetamine and l-amphetamine by microsomal preparations of rabbit, guinea pig and rat were found to implicate oxidation on the nitrogen to give alpha-methyl beta-phenethylhydroxylamine as the metabolic route which then leads to syn and anti-phenylacetone oximes. Only small amounts of phenylacetone oxime (anti- and syn forms) were present after incubation of amphetamine. It is concluded that microsomal enzymatic attack on amphetamine about the N-center occurs by two routes: (1) on the carbon at the alpha position to the N-atom to give the alpha-carbinol amine and (2) on the N-atom to give the N-oxide which by proton transfer becomes the hydroxylamine. 3 references.

113360 Barlow, R.B.; Reading, H.W.; Yates, Celia M. Department of Pharmacology, University of Edinburgh, Edinburgh, Scotland Distribution and excretion of N-(14C)-methyl labelled m-hydroxybenzyltrimethylammonium ions in mice. ***British Journal of Pharmacology (London).*** **44(3):577-582, 1972.**

Radioactivity in the plasma, livers, and brains of mice was measured at intervals of 10 min to 24 h after the intraperitoneal injection of 14C labelled m-methoxybenzyltrimethylammonium ions and m-hydroxybenzyltrimethylammonium

ions. Well over 10% of the dose of either of these quaternary compounds was found in the liver and plasma within 10 min of the injection, but they were rapidly excreted or metabolized, having a half life of between 1 and 2 hours. Small amounts of radioactivity were detectable in brain, and were not due to contamination of brain samples by blood, after doses of 14-16 micro mol/kg (approximately 4mg iodide/kg) and upwards. After doses of 4-6 micro mol/kg (approximately 1mg iodide/kg), however, radioactivity in the brain was barely detectable. Any behavioral effects reported to occur in mice treated with these lower doses of m-hydroxybenzyltrimethylammonium, which include improved performance in a test of avoidance learning, are unlikely to be due to an action within the central nervous system. Learning may be more influenced by the peripheral effects of drugs than has hitherto been appreciated. 5 references. (Author abstract)

113362 Hamilton, T.C. Pharmacology Department, Roche Products Ltd., Welwyn Garden City, Herts, England Effects of dopamine on the conductance of perfused vascular beds of the chloralosed cat. ***British Journal of Pharmacology (London).*** **44(3):442-450, 1972.**

Dopamine produced vasoconstriction followed by secondary vasodilatation in the perfused cat hindquarters and splanchnic region. Low doses produced only vasodilatation in the splanchnic region. Phenoxybenzamine abolished, while desipramine and cocaine potentiated, the vasoconstrictor and secondary dilator actions of dopamine. After phenoxybenzamine, dopamine produced only vasodilatation in both the hindquarters and splanchnic region, being more effective in the latter. Haloperidol, but not propranolol, atropine or mepyramine, antagonized dopamine induced vasodilatation. Dopamine differs from other catecholamines in that, while its cardiac effects are mediated by a beta adrenoceptive mechanism, its vasodilator effects are not. The results support the concept of a specific receptor mediating dopamine vasodilatation. 17 references. (Author abstract modified)

113374 Modigh, K. Department of Pharmacology, University of Goteborg, Goteborg, Sweden Central and peripheral effects of 5-hydroxytryptophan on motor activity in mice. ***Psychopharmacologia (Berlin).*** **23(1):48-54, 1972.**

Spontaneous motor activity was studied in mice given DL-5-hydroxytryptophan (5-HTP) i.p.in doses ranging from 6.25 to 800mg/kg with and without previous administration of L-alpha-hydrazino-alpha-methyl-beta-(3,4-dihydroxyphenyl)propionic acid (MK-486), an inhibitor of peripheral amino acid decarboxylase. Some mice were also given repeated injections of DL-alpha-methyl-metatyrosine (alpha-MMT) prior to MK-486 and 5-HTP. The brain levels of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) were also determined in these animals. 5-HTP in doses between l00 and 800mg/kg caused a decrease in motor activity when given along, whereas after pretreatment with MK-486 it increased motor activity. Lower doses of 5-HTP, alone or in combination with MK-486, had no significant effect on motor activity. Pretreatment with MMT caused a marked depletion of NA and DA without counteracting the increase in motor activity induced by MK-486 and 5-HTP. The central effects of large doses of 5-HTP are excitatory, whilst the effects outside the blood - brain barrier have an inhibitory influence on the motor activity in mice. The mechanisms for the central excitatory effects are discussed. 23 references. (Author abstract modified)

113375 Kabes, Jan; Fink, Zdenek; Roth, Zdenek. Purkyne Medical Research Institute, Hradec Kralove, Czechoslovakia A new device for measuring spontaneous motor activity -- effects of lysergic acid diethylamide in rats ***Psychopharmacologia (Berlin).*** **23(1):75-85, 1972.**

By means of a new automatic apparatus the influence of lysergic acid diethylamide (LSD) on spontaneous motor activity (SMA) was investigated in rats. Both the horizontal and vertical component of SMA were registered simultaneously at various time intervals after i.p.administration of the drug. A biphasic effect of LSD on both parameters was observed -- SMA was stimulated in the first phase, while an inhibitory effect appeared with the increasing interval from the drug administration. The horizontal component was found to be more sensitive to the stimulatory effect while inhibition was more marked in the vertical activity. 26 references. (Author abstract)

113378 Tonge, Sally R.; Leonard, Brian E. School of Pharmacy, The Polytechnic, Byrom St., Liverpool 3, U.K. Interaction of phencyclidine with

drugs affecting noradrenaline metabolism in the rat brain. *Psychopharmacologia (Berlin).* 23(1):86-90, 1972.

The effects of phencyclidine, tetrabenazine and desipramine, alone and in combination, on the levels of noradrenaline and normetanephrine were determined in the forebrains, midbrains and hindbrains of rats. Phencyclidine alone decreases both noradrenaline and normetanephrine concentrations and appears to antagonize the elevation of normetanephrine levels produced by 5mg/kg of desipramine. A combination of tetrabenazine (40mg/kg) and desipramine (5mg/kg) produced a 40-50% depletion of noradrenaline from all 3 areas of the brain, accompanied by increased normetanephrine levels; phencyclidine antagonized the depletion of noradrenaline, but further increased normetanephrine levels. 8 references. (Author abstract)

113456 Jacob, J.; Girault, J.M.; Peindaries, R. Service de Pharmacologie, Institut Pasteur, Paris 15, France Actions of 5-hydroxytryptamine and 5-hydroxytryptophan injected by various routes on the rectal temperature of the rabbit. ***Neuropharmacology (Oxford).*** **11(1):1-16, 1972.**

By systemic, intracisternal or intracerebroventricular routes, graded doses of 5-hydroxytryptamine (creatinine sulphate or hydrogen maleinate) and of D,L-5-hydroxytryptophan elicited the same general pattern of effects on the temperature of wake rabbits: falls in temperature which were gradually superceded by rises in temperature. The effective dosages were much lower when the drugs were injected into the CSF than when administered systematically. Effects obtained by the intracisternal and by the intracerebroventricular routes were similar. Inhibition of monoamine oxidases by phenylisopropylhydrazine resulted in marked potentiation of falls and rises observed after amine or amino acid injection into the CSF: the falls, however, occurred rarely. After systemic injection, temperature rises were potentiated, but the falls were not. The effectiveness of amine and amino acid administration by different routes, and before and after monoamine oxidase inhibition, are discussed. The present results stress that dual direction of the central thermic effects of exogenous and endogenous 5-hydroxytryptamine, and give some support to its possible participation in pharmacological and physiological variations in the temperature of the rabbit. 23 references. (Author abstract modified)

113460 Fibiger, H.C.; Trimbach, C.; Campbell, B.A. Div.of Neurological Sciences, Dept.of Psychiatry, Univ.of British Columbia, Vancouver, 8, B.C., Canada Enhanced stimulant properties of d-amphetamine after chronic reserpine treatment in the rat: mediation by hypophagia and weight loss. ***Neuropharmacology (Oxford).*** **11(1):57-67, 1972.**

The enhanced stimulant properties of d-amphetamine were studied in rats after chronic reserpine treatment. Twenty four hours after last reserpine or saline treatment, rats were given d-amphetamine or saline and their locomotor activity was measured for 3 hr. In accordance with previous reports, d-amphetamine induced a significantly greater stimulation of spontaneous activity after reserpine. The effect was variable however insofar as it was observed only in those animals that suffered marked weight loss during the reserpine treatment. In addition, when the heightened baseline activity of the groups chronically treated with reserpine was considered, the enhanced stimulant effects of d-amphetamine were no longer evident. In a second experiment, the food intake of the chronic saline animals was controlled so that both the reserpine and saline groups underwent similar weight losses during the 10 day injection procedure. In that experiment, chronic reserpine treatment failed on every measure to increase the stimulant effect of d-amphetamine. In contrast to the first experiment, on one measure (the lowest dosage which significantly increased activity) the saline pretreated animals were more responsive to d-amphetamine than were the rats pretreated with reserpine. It is suggested that chronic reserpine administration continues to exert a mild sedative action which is completely masked and reversed by the marked increase in arousal which results from the reserpine mediated hypophagia and weight loss. This starvation induced arousal appears to interact with amphetamine mediated locomotor stimulation to produce the increased responsiveness to amphetamine after chronic reserpine treatment. 18 references. (Author abstract modified)

113467 Korf, J.; van Praag, H.M. Dept.of Biological Psychiatry, Psychiatric Univ.Clinic, Oostersingel 59, Groningen, The Netherlands Action of p-chloroamphetamine on cerebral serotonin metabolism: an hypothesis. ***Neuropharmacology (Oxford).*** **11(1):141-144, 1972.**

The effect of p-chloroamphetamine (4CA) on the turnover of cerebral 5-hydroxytryptamine (5-HT) in the mouse was studied. It was found that

4CA in relatively low doses altered the turnover of 5nHT in the mouse brain, but did not decrease the 5-HT levels. In higher doses, 4CA depleted the 5-HT levels in the mouse brain. The finding that 4CA decreased the turnover rate of 5-HT supports the hypothesis that activation of central 5-HT receptors diminished the turnover rate. The action of 4CA on a cellular level is still obscure. A literature study suggests that 4CA inhibits the synthesis or metabolism of serotonin and these concepts are discussed in relation to the study. 12 references.

113468 Palmer, G.C. Dept.of Pharmacology, School of Medicine, Univ.of New Mexico, Albuquerque, N.M. 87106 Increased cyclic AMP response to norepinephrine in the rat brain following 6-hydroxydopamine. ***Neuropharmacology (Oxford).*** **11(1):145-149, 1972.**

A study to determine if there is an enhanced cyclic adenosine 3',5' monophosphate (AMP) response to norepinephrine in vitro in different rat brain areas following in vivo injections of 6-hydroxydopamine is reported. Rats were injected intraventricularly with either 6-hydroxydopamine (250 micrograms per day for 2 days) or a control solution. Seven days later the animals were killed and slices from the hypothalamus, brain stem cerebrum and cerebellum were incubated in vitro in the presence of norepinephrine. After 6 min exposure to norepinephrine there were enhanced cyclic AMP levels in the hypothalamus, cerebrum and brain stem of animals treated with 6-hydroxydopamine when compared to controls. These results suggest that adrenergic denervation supersensitivity to catecholamines may be mediated by adenyl cyclase. 11 references. (Author abstract modified)

113534 Milner, Joel S. Western Carolina Univ., Cullowhee, N.C. 28723 Anticholinergic blockage of water intake in the Mongolian gerbil. ***Psychonomic Science.*** **26(3):135-136, 1972.**

The effects of a centrally active cholinergic blocking agent, atropine sulfate, and its centrally inactive quaternary analog, atropine methyl nitrate, on water intake in the Mongolian gerbil were examined. Interperitoneal of atropine sulfate and atropine methyl nitrate produceda drug and dose dependent decrease in drinking in water deprived gerbils. Water intake was more effectively blocked by atropine sulfate than by atropine methyl nitrate. Nevertheless, as both drug dosages increased, water intake decreased. These data support findings in the rat which indicate that drinking is mediated by cholinergically controlled central mechanisms. In addition, however, effective blockage by centrally inactive atropine methyl nitrate suggests that peripheral cholinergic systems also play a role in regulating drinking behavior in the gerbil. 11 references. (Author abstract modified)

113544 Landmark, Knud; Haffner, Jon F.W.; Setekleiv, Johannes. Institute of Pharmacology, Univ.of Oslo, Blindern, Oslo 3, Norway Reduction in 42K-efflux from rat atria by promazine and thioridazine. ***Acta Pharmacologica et Toxicologica (Kobenhavn).*** **31(1-2):54-64, 1972.**

The reduction in 42K-efflux from rat atria by promazine and thioridazine was examined. It was shown that promazine and thioridazine cause a dose dependent decrease in 42K-efflux from electrically stimulated rat atria. Promazine is the more potent drug when compared on a molar basis. Results indicate that the drug changes the membrane permeability for K ion and that the decrease in the atrial contractile force can be dissociated from this effect. 27 references. (Author abstract modified)

113558 Maj, Jerzy; Grabowska, Maria; Gajda, Lucyna. Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland Effect of apomorphine on motility in rats. ***European Journal of Pharmacology (Amsterdam).*** **17(2):208-214, 1972.**

Apomorphine, which stimulates central dopamine receptors, was used to study the role of dopaminergic systems in motility changes in rats. Motility was measured by a photocell method. Apomorphine induced increase in motility was blocked by haloperidol, spiroperidol, or phenoxybenzamine, but not by reserpine. The effect of apomorphine was partly inhibited by alpha-methyltyrosine, dimethyldithiocarbamate and disulfiram in both normal and reserpinized rats. It was potentiated by nialamide given with L-DOPA, but not by nortriptyline, desipramine, or cocaine. Apomorphine increases the motility in rats by direct stimulation of dopamine receptors but another factor is also of importance: noradrenergic neurotransmission. Both dopamine and noradrenaline neurones are probably involved in the control of motility in rats. 27 references. (Author abstract)

113562 Fuentes, J.A.; Del Rio, J. Department of Medicinal Chemistry, Institute of Organic Chemistry, C.S.J.C., Madrid 6, Spain Striatal homovanillic acid levels in rats after combined treatments with amphetamine and neuroleptics. *European Journal of Pharmacology (Amsterdam).* 17(2):297-300, 1972.

In rats, d-amphetamine, 10mg/kg, antagonized the rise of striatal homovanillic acid induced by chlorpromazine, 4mg/kg, and potentiated the rise induced by triperidol, 0.25mg/kg. The results suggest that different mechanisms may be involved in the mode of action of these 2 neuroleptics at the level of brain dopaminergic receptors. 25 references. (Author abstract modified)

113564 Smythies, J.R.; Beaton, J.M.; Benington, F.; Morin, R.D. Department of Psychiatry, University of Alabama Medical Center, Birmingham, Alabama The design of some new compounds to block psychotomimetic drugs. *European Journal of Pharmacology (Amsterdam).* 17(2):270-272, 1972.

It was predicted from theory that: 1) N,N-diethylacetamide (DAA) would not, but 2) N,N-diethylbutyramide (DBA) would block dimethyltryptamine (DMT) and 3) DBA would not block mescaline or 2,5-dimethoxy-4-methylamphetamine (DOM). Experiments using the Bovet - Gatti profiles in rats confirmed these predictions. DBA may be of clinical use in combatting the psychoses induced by abuse of LSD and similar compounds. 5 references. (Author abstract modified)

113565 Wallach, M.B.; Friedman, E.; Gershon, S. Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, N.Y. 10016 Behavioral and neurochemical effects of psychotomimetic drugs in neonate chicks. *European Journal of Pharmacology (Amsterdam).* 17(2):259-269, 1972.

The effects of various psychoactive drugs on the behavior and brain neurochemistry of neonate chicks were examined. d-Amphetamine, l-amphetamine, p-hydroxyamphetamine, and l-dopa all elicited a similar behavioral excitement. Mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM) caused opisthotonic postures. Cocaine and p-methoxyamphetamine induced some features of both groups and cocaine also elicited convulsions. Norepinephrine and dopamine produced sedation. All agents inducing opisthotonos elevated brain norepinephrine. d-Amphetamine and l-dopa reduced serotonin while norepinephrine, dopamine and DOM all elevated serotonin. Dopa doubled the brain dopamine levels while norepinephrine reduced them. Paradoxes in the data are discussed. 33 references. (Author abstract)

113570 Rosner, H. Zoologisches Institut der Universitat, D-4400 Munster, Hindenburgplatz 55, Germany /Action of chlorpromazine in the Teleost CNS. II. Uptake and distribution of 35S-chlorpromazine and its binding to components of the neuroplasm./ Untersuchungen zur Wirkung von Chlorpromazin im ZNS von Teleosteern. II. Aufnahme und Verteilung von 35S-Chlorpromazin sowie Bindung an Neuroplasmakomponenten. *Psychopharmacologia (Berlin).* 23(2):136-151, 1972.

Uptake and distribution of 35S-chlorpromazine (35S-CP) in the nervous system of Brachydanio rerio (Teleosts) and the optic tract of Carassius carassius (Teleosts) were investigated by means of autoradiography and liquid scintillation counting. In addition, the ability of the drug to form complexes with soluble neuronal cell components was demonstrated in Scardinius erythrophthalmus (Teleosts) using the gel filtration method. Following percutaneous application, 35S-CP was rapidly taken up by the brain. There was no evidence for a blood - brain barrier for the drug in all brain areas examined and uptake continued in a linear manner over the whole incorporation period of 6 h. In the optic tectum as well as in the cerebellum the labelling of the nerve fibres exceeded that of the cell bodies. After injection into the eye, 35S-CP (probably bound to protein) was transported down the optic tract at a rate of 1-2 mm/d. Supernatants of brain homogenates contained at least 2 different soluble components separable from each other into a protein and a nonprotein fraction by gel filtration, each able to form a complex with CP in vitro. The findings further support the supposition that the pharmacological and physiological effects of the drug are brought about by its special ability to form complexes with various neuronal cell components. 25 references. (Author abstract)

113571 Rosner, H. Zoologisches Institut der Universitat, D-4400 Munster, Hindenburgplatz 55, Germany /Action of chlorpromazine in the Teleost CNS. I. Effects on behavior and the incorporation of 3H-uridine and 3H-histidine./ Untersuchungen zur Wirkung von Chlorpromazin im ZNS von

Teleosteern. I. Einfluss auf das Normalverhalten sowie den Einbau von 3H-Uridin und 3H-Histidin. ***Psychopharmacologia (Berlin).*** **23(2):125-135, 1972.**

The influence of chlorpromazine (CP) on the incorporation of 3H-uridine into (RNA) and 3H-histidine into proteins of the optic tectum was investigated in Brachydanio rerio (Teleosts) by means of autoradiography. In addition, the effect of different concentrations of the drug (1-128mg CP/1 bathing medium) on the behavior of the fish was examined. The LD50 was 2mg CP/1.1.5mg CP/1, a sublethal dose which induces behavior changes, slightly inhibited RNA synthesis. On the other hand, the same dose has a marked effect on protein metabolism; both total incorporation of 3H-histidine into the cell bodies as well as protein breakdown in the nerve fibers appeared to be inhibited as indicated by a decreased labelling of the pericarya after short periods and an increased accumulation of label in the nerve fibers after long periods of incorporation. Moreover the 3H-histidine labelling in the optic tectum was less affected by exogenous protease in CP treated animals than in controls. The possible sites of action of the drug are discussed. 20 references. (Author abstract modified)

113572 Schrold, J. Institute of Pharmacology, Odense University, Niels Bohrs alle, DK-5000 Odense, Denmark Behavioural effects of d-amphetamine alone and in combination with antidepressants, antihistamines or other psychotropic drugs in young chicks. ***Psychopharmacologia (Berlin).*** **23(2):115-124, 1972.**

Antidepressants, antihistamines or other psychotropic drugs were administered before injection of d-amphetamine in 3-5 day old chicks. This pretreatment completely protected some animals against the characteristic behavioral changes seen after d-amphetamine 6mg/kg i.p. In addition chlorpheniramine, chlorimipramine, imipramine, cocaine, and diphenhydramine were also able to antagonize a dose of 10mg/kg i.p. It was further noticed that well developed d-amphetamine symptoms were interrupted by subsequent treatment with imipramine. 23 references. (Author abstract)

113642 Kellogg, C.; Lundborg, P. Department of Pharmacology, Fack, S-40033 Goteborg 33, Sweden Ontogenic variations in responses to L-DOPA and monoamine receptor-stimulating agents. ***Psychopharmacologia (Berlin).*** **23(2):187-200, 1972.**

The spontaneous motor activity, overt behavioral responses, and concentration of noradrenaline (NA) and dopamine (DA) in the brain were studied in young rats at different postnatal ages following the administration of L-DOPA (100mg/kg) or NA and DA receptor stimulating or blocking agents. L-DOPA induced marked hyperactivity even at one day of age and the duration of the L-DOPA-induced hyperactivity and increase in NA and DA concentrations in the brain decreased with ontogenic development. At 21 days, the apparent behavioral response to L-DOPA was one of depression rather than marked excitation. Pretreatment of 21 day old animals with MK-486, a peripheral decarboxylase inhibitor, produced excitation with aggressive responses, whereas in younger animals the effect of this drug was only to lengthen the duration of the response. It was concluded that not until around 21 days of age does the capacity of the peripheral decarboxylase become a major factor in determining the behavioral response to L-DOPA. Clonidine, a NA receptor stimulating agent elicited behavioral responses from one day of age similar to the responses observed after L-DOPA. A response to apomorphine, a DA receptor stimulating agent, was not readily observed until 4 days of age and then the response was rather variable. Marked stereotyped behavior was not observed in response to apomorphine until 21 days of age. This difference between clonidine and apomorphine stimulation suggests that NA receptors may develop at an earlier age than DA receptors. 26 references. (Author abstract)

113645 Kamat, Usha G.; Pradhan, Ratan J.; Sheth, U.K. Dept.of Pharmacology, Seth G.S.Medical College, Parel, Bombay 12, India Potentiation of a non-narcotic analgesic, dipyrone, by cholinomimetic drugs. ***Psychopharmacologia (Berlin).*** **23(2):180-186, 1972.**

Dipyrone analgesia in mice was potentiated by physostigmine, neostigmine, and pilocarpine. This potentiation was antagonized by atropine sulfate and atropine methyl nitrate. Tremorine and dextroamphetamine which implicate brain monoamines in their analgesic effects, were inactive, as were carbachol and nicotine. Hydroxyzine did not potentiate dipyrone analgesia, ruling out a (CNS) depressant component in dipyrone potentiation. Dipyrone which has central analgesic and parasympathomimetic effects is specifically potentiated by cholinergic drugs. Such potentia-

tion of a nonnarcotic analgesic by cholinergic agents argues against a specific involvement of cholinergic receptors in narcotics analgesia (and/or other narcotics' actions) and may indicate a cholinergic involvement in pain mechanisms and/or central analgesic effects without specific reference to narcotics. 28 references. (Author abstract modified)

113724 Krieglstein, J.; Meiler, W.; Staab, J. Dept.of Pharmacology, Univ.of Mainz, D 65 Mainz, Germany Hydrophobic and ionic interactions of phenothiazine derivatives with bovine serum albumin. *Biochemical Pharmacology (Oxford).* 21(7):985-997, 1972.

The binding of promethazine, trimeprazine, desmethylpromazine, desmethylchlorpromazine and perazine to bovine serum albumin was measured by sephadex gel filtration and equilibrium dialysis. The binding of these drugs to albumin is characterized by the following parameters: percentage of bound drug, the association constant K1, the apparent binding constant, and the free energy. In addition, the displacing activity of hydroxyzine and acetylsalicylic acid on the binding of phenothiazines to albumin was examined. The binding of phenothiazine derivatives to bovine serum albumin is correlated with their octanol - water partition coefficients. The results allow the following interpretation of the phenothiazine - albumin complex. Only one of the phenothiazine benzene rings is attached to a hydrophobic area on the albumin molecule, while the basic dimethylamino group is associated with a negatively charged group on the protein surface. The aliphatic side chian obviously does not directly take part in binding. But a methyl group in the aliphatic chain as in the case of promethazine or trimeprazine enhances the binding of the molecule significantly. 28 references. (Author abstract)

113800 Dorman, R.M.; Harner, R.N. Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa. Behavioral and EEG effects of disulfiram. *Psychophysiology.* 9(1):91-92, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that administration of disulfiram (250mg/kg/ i.p.)to 12 male cats, chronically implanted with cortical, caudate and hippocampal electrodes, revealed long lasting behavioral and EEG effects. Early agitation, blinking, mydriasis, relaxation of nictitating membranes and drooling were attributed to nonspecific sympathetic effects. EEG desynchronization persisted for an average of 1 to 2 hrs while the animal remained quiescent and often assumed a lateral recumbent posture. Frequent transitions from the waking state into desynchronized sleep (DS) were signaled by abrupt loss of neck tone, the appearance of a sleeping posture and continuing EEG desynchronization. These transitions were often punctuated by bursts of tonic muscular activity. REMs were absent in more than half of these DS episodes, which in other details resembled narcoleptic transitions in man. After 3 to 6 hrs, slow wave sleep predominated by DS (now, the majority with REMs) still accounted for 30 to 40% of the recording time. Disulfiram blocks beta hydroxylation of dopamine, producing a decrease in brain norepinenephrine generally, and an increase in hypothalamic dopamine. In this light, the study lends further support to the suggestion of a major physiologic role for dopamine in EEG desynchronication associated with arousal and DS. (Journal abstract modified)

113900 Crossland, J.; Turnbull, M.J. Pharmacology Laboratories, The University, Nottingham NG7 2RD, U.K. The effect of the chronic administration of barbitone on the growth rate of the rat. *Neuropharmacology (Oxford).* 11(2):163-176, 1972.

Experiments designed to study the barbiturate dependence in rats are discussed. Young rats received sodium barbitone, in progressively increasing amounts, in their drinking water over a period of 4 or 5 weeks. They gained weight more rapidly than litter mates that were not given the drug. They did not retain more water or lay down more fat than untreated animals and a comparison of their body composition and skeletal lengths with those of older, untreated animals made it clear that sodium barbitone administration actually stimulated skeletal growth in young rats. It was without effect in adult animals. 19 references.(Author abstract modified)

113901 Roberge, Andree G.; Missala, Krystyna; Sourkes, T.L. Laboratories de Neurobiologie, Faculte de Medecine, Universite Laval, Quebec, Canada Alpha-methyltryptophan: effects on synthesis and degradation of serotonin in the brain. *Neuropharmacology (Oxford).* 11(2):197-209, 1972.

Alpha-methyltryptamine and alpha-methylserotonin have been detected in rat brain following the administration of doses of AMTP (alpha-methyltrytophan) of 50mg/kg or greater. At 4-6 hr after a single injection of AMTP the concentration of alpha-methyltryptamine was very much smaller that that of alpha-methylserotonin. The concentration of the latter substance was followed as a function of time after the administration of AMTP. There was a gradual increase of alpha-methylserotonin and decrease of serotonin so that the concentration of alpha-methylserotonin rose to 6 times that of the naturally occurring amine in 48 hr, falling to 3 times its concentration in 96 hr. Control levels of 5-hydroxyindoleacetic acid and of material measured fluorometrically as serotonin were evetually attained 8-10 days after the injection of AMTP. The influence of AMTP on the concentrations of brain 5-hydroxyindoleacetic acid and serotonin like substances (serotonin and alpha-methylserotonin) was studied in relation to the actions of various drugs. Treatment of rats with sufficient p-chlorophenylalanine to lower the concentration of serotonin and 5-hydroxyindoleacetic acid in the brain by 50% did not prevent the appearance of substantial amounts of alpha-methylserotonin in the brains of AMTP treated animals. On the other hand, the decarboxylase inhibitors Ro4-4602 and NSD-1055, both prevented formation of alpha-methylserotonin from AMTP. Reserpine, 2 monoamine oxidase inhibitors, and probenecid were also tested for interaction with AMTP. The results with respect to cerebral 5-hydroxyindoleacetic acid were generally interpretable on the basis of independent actions of the drugs. 34 references. (Author abstract modified)

113902 Segal, M.; Deneau, G.A.; Seevers, M.H. Department of Pharmacology, Faculty of Med., Dalhousie Univ., Halifax, Nova Scotia, Canada Levels and distribution of central nervous system amines in normal and morphine-dependent monkeys. ***Neuropharmacology (Oxford).*** **11(2):211-222, 1972.**

The distribution of norepinephrine, dopamine, and 5-hydroxytryptamine in various areas of the central nervous system (CNS) of the normal monkey is presented. The central levels and distribution of norepinephrine, dopamine, and 5-hydroxytryptamine were determined after single doses of morphine, during maintenance of physical dependence and following withdrawal from chronic administration of morphine. Small and nonstressful doses of morphine were employed to induce experimental physical dependence. Alpha-methyl-DOPA did not qualitatively or quantitatively alter the abstinence syndrome. Pretreatment with iproniazid did not prevent depression produced by single doses of morphine in the nontolerant monkey. The data observed in this study offer no support for the view that gross behavioral changes in the monkey produced by morphine or by its withdrawal after the development of physical dependence are induced by or may be correlated with changes in amine levels in the CNS. 37 references. (Author abstract)

113903 Dreyfuss, J.; Beer, B.; Devine, D. D.; Roberts, B.F.; Dreyfuss, J.; Beer, B.; Devine, D. D.; Roberts, B.F.; Schreiber, E.C. Departments of Drug Metabolism and Pharmacology, Squibb Institute for Medical Research, New Brunswick, New Jersey 08903 Fluphenazine - induced Parkinsonism in the baboon: pharmacological and metabolic studies. ***Neuropharmacology (Oxford).*** **11(2):223-230, 1972.**

Drug induced Parkinsonism in the baboon was studied. Extrapyramidal signs were produced in baboons following the oral administration of 1.5-5mg/kg per day of fluphenazine dihydrochloride. The drug induced extrapyramidal signs included tremors at rest or in motion, motor retardation, masque facies, rigidity, and salivation. Administration of the antiparkinson agents benztropine mesylate or trihexyphenidyl hydrochloride was ineffective in reversing the extrapyramidal signs when these agents were given together with fluphenazine. 7-Hydroxyfluphenazine, a metabolite of fluphenazine in the baboon, was at least 500 times less active than fluphenazine in producing depression and did not produce extrapyramidal signs. Metabolic studies with fluphenazine-14C in the baboon indicated that the biological disposition of the drug resembles that seen previously in the rhesus monkey. The plasma half-life for the elimination of fluphenazine-14C, its metabolites, or both, agrees roughly with the length of time required for extrapyramidal signs to disappear after withdrawal of the drug.13 references.(Author abstract modified)

113906 Bohdanecky, Z.; Radit-Weiss, T.; Skvaril, J. Institute of Psychology and Institute of Physiology, Czechoslovak Academy of Sciences, Prague, Czechoslovakia The effect of (plus)-phenmetrazine

upon reticular unit activity. *Neuropharmacology (Oxford).* 11(2):273l282, 1972.

The effect of i.p.administration of (d)-phenmetrazine (2 and 5mg/kg) on the unit activity of the mesencephalic reticular formation was studied in rats. The activity of 123 neurones was evaluated statistically with a computer. The neurones were divided into 6 classes according to type of reaction. The drug treated neurones showed a number of changes approximately 15-20 min after drug administration, while 35% of saline neurones remained unaffected. Most of the changes (over 50%) in drug treated groups were due to inhibition of the firing of reticular neurones. 14 references. (Author abstract modified)

113908 Costa, E.; Revuelta, A. Laboratory of Preclinical Pharmacology, NIMH, St. Elizabeth's Hospital, Washington, D.C. 20032 (-)-p-Chloroamphetamine and serotonin turnover in rat brain. ***Neuropharmacology (Oxford).*** **11(2):291-295, 1972.**

In rats, the injection of 25micromol/kg i.p.of (-)-p-chloroamphetamine decreased the concentration of serotonin (5-HT) in the tel-diencephalon by about 70%. This dose was less active in decreasing the 5-HT content of either the hypothalamus or brainstem. This amphetamine analogue reduced the turnover rate of tel-diencephalic 5-HT more than the indolealkylamine turnover in the brainstem. Various reasons for the localization of the action of p-chloroamphetamine to selected brain areas are considered. (Author abstract modified)

113909 Bennett, J.M. Department of Pharmacy, University of Aston, Birmingham 4, England Modification of strychnine-induced convulsions by anticonvulsants in the frog. ***Neuropharmacology (Oxford).*** **11(2):297-299, 1972.**

In frogs, short-term pretreatment with reserpine (amine release) prevented sustained convulsions, whereas long-term pretreatment (amine depletion) prolonged the convulsions, induced by strychnine. In ascending order of potency, chlorpromazine (a tranquillizer), mephenesin (a centrally acting muscle relaxant), and orphenadrine (an antidepressant) caused such convulsions to be discontinuous. The duration of the most prolonged convulsion is given as the most suitable parameter for assessing anticonvulsive activity using the partly decerebrate frog. 10 references. (Author abstract modified)

113978 Samanin, R.; Valzelli, L.; Gumulka, W. Istituto di Richerche Farmacologiche 'Mario Negri', Via Eritrea 62, I-20157 Milan, Italy Inhibitory effect of midbrain raphe stimulation on cortical evoked potential in rats. ***Psychopharmacologia (Berlin).*** **24(3):373-379, 1972.**

The effect of midbrain raphe (MR) stimulation on peripherally evoked cortical potentials was studied in rats. Stimulation of the MR induced a decrease of the peripherally evoked potentials in the primary sensory cortex. The inhibition was blocked by relatively small doses of strychnine whereas picrotoxine was ineffective. Low doses of LSD-25, markedly potentiate the effect of MR stimulation. 23 references. (Author abstract modified)

113979 Dhasmana, K.M.; Dixit, K.S.; Jaju, B.P.; Gupta, M.L. N.V.Philips-Duphar, Post bus 2, Weesp, The Netherlands Role of central dopaminergic receptors in manic response of cats to morphine. ***Psychopharmacologia (Berlin).*** **24(3):380-383, 1972.**

The administration of morphine in conscious cats produces a manic response characterized by hyperexcitement and aggressive behavior. This manic response was prevented by pretreatment of cats with either central nervous system (CNS) depletors (reserpine and tetrabenazine) or central dopaminergic receptor blocking agents (haloperidol and chlorpromazine). On the other hand, alpha and beta adrenergic receptor blocking agents phenoxybenzamine and propranolol did not antagonize the morphine mania. Similarly, anticholinergic (atropine), antihistaminic (mepyramine) and antiserotonin (LSD-25) agents did not prevent morphine mania. It is concluded that morphine releases dopamine in the CNS which in turn excites the central dopaminergic receptors to induce the manic response. 12 references. (Author abstract)

113981 Herman, Zbigniew S.; Kmieciak-Kolada, Krystyna; Brus, Ryszard. Dept.of Pharmacology, Silesian School of Medicine, Zabrze 8, Marksa 38, Poland Behaviour of rats and biogenic amine level in brain after 6-hydroxy-dopamine. ***Psychopharmacologia (Berlin).*** **24(3):407-416, 1972.**

Male, Wistar rats were injected into the right lateral ventricle of the brain with 6-hydroxydopamine (6-OHDA). The behavior of animals and the level of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) were mea-

sured after different periods of time. During the first hour after 6-OHDA injection the behavior of rats was similar to that observed after reserpine or a benzoquinolizine derivative; 6 h after the drug injection signs of sedation occurred. Twenty four and 48 h after 6-OHDA treatment locomotor activity of rats was similar to the activity of untreated animals. Sixty eight h after 6-OHDA application a decrease of exploratory activity was noted. Seven h after 6-OHDA treatment a decrease of NA level was observed in the cortex, mesencephalon, thalamus and hypothalamus but an increase of NA content in the striatum. Three days after 6-OHDA injection a decrease of the NA content in the cortex, thalamus and hypothalamus was seen. The DA level increased in most of the examined areas 7 h after 6-OHDA application; 3 days after the drug injection the DA level decreased in hypothalamus, thalamus and striatum and did not change in other brain areas. The 5-HT level increased in the pons and medulla oblongata and decreased in the mesencephalon 7 h after 6-OHDA injection and was unchanged in all examined structures 3 days after 6-OHDA application. These biochemical changes in the brain were not correlated with the behavioral changes of rats. 24 references. (Author abstract)

113983 Selye, Hans; Szabo, Sandor. Institut de Medicine et de Chirugie experimentales, Univ.de Montreal, Montreal 101, Quebec, Canada Protection against haloperidol by catatoxic steroids. ***Psychopharmacologia (Berlin).*** **24(3):430-434, 1972.**

A study of protection against haloperidol in the rat by catatoxic steroids is reported. Experiments on rats show that the effect of haloperidol upon central nervous system activity is abolished or inhibited by pregnenolone-16alpha-carbonitrile (PCN), 'Catatoxic Steroid Number 1' (CS-1), ethylestrenol, spironolactone, norbolethone, oxandrolone, prednisolone and, to a lesser extent, by progesterone. On the other hand, triamcinolone and thyroxine actually increase the sensitivity of the rat to haloperidol so that normally well tolerated doses induce a high mortality. Since the protective effect of the above mentioned steroids against most toxicants is ascribed to hepatic microsomal enzyme induction, it is of special interest that phenobarbital -- one of the most potent nonsteroidal hepatic mircosomal enzyme inducers -- fails to protect the rat against haloperidol. These findings confirm earlier observations which showed that there are great qualitative differences between the protective effects of various enzyme inducers upon diverse substrates. 10 references. (Author abstract modified)

113984 Echols, Stanley D.; Jewett, Robert E. Dept.of Pharmacology, Emory Univ.Atlanta, Ga. 30322 Effects of morphine on sleep in the cat. ***Psychopharmacologia (Berlin).*** **24(3):435-448, 1972.**

The effects of morphine sulfate on the sleep of cats was studied by electroencephalographic techniques. In contrast to placebo experiments the animals were awake for approximately 6 h after administration of morphine; the return of regular sleep patterns occurred after about 11 h. A rebound increase in rapid eye movement (REM) sleep time and percentage was noted during the 11th through the 17th hour of the study. Sleep following manual sleep deprivation for the 10 h showed a rebound increase in REM and non rapid eye movement (NREM) sleep time. NREM sleep rebound after manual sleep deprivation exceeded that occurring after morphine. The alerting actions of morphine could be blocked by naloxone for about 90 min. Naloxone alone increased REM sleep time and percentage. Single (84 mg/kg) or multiple (51 mg/kg for 4 injections) doses of dl-alpha-methyltyrosine i.p.did not block the alerting action or REM sleep rebound caused by morphine. 5-Hydrotryptophan did not antagonize the alerting action of morphine. 28 references. (Author abstract)

113986 Shah, Nandkumar S.; Alpers, H.S.; Himwich, H.E. Ensor Research Laboratory, Wm S.Hall Psychiatric Institute, P.O.Box 119, Columbia, S.C. 29202 Regional localization of 3,4-dimethoxyphenylethylamine-14C (DMPEA-14C) in rabbit brain: effects of reserpine and iproniazid pretreatment. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(1):144-150, 1972.**

The distribution and metabolism of 3,4-dimethoxyphenylethylamine-14C (DMPEA-14C) in rabbit brain 1 hr.after i.v.administration was investigated. The 14C was unevenly distributed into various regions with the highest level in the caudate nucleus and the lowest in the superior colliculus. All 11 brain areas studied were active in oxidative deamination of injected DMPEA. The levels of total radioactivity in the caudate nucleus, inferior colliculus, thalamus and hypothalamus were about 2 to 2.5times that in the superior colliculus. The levels of unchanged amine in these areas and the medulla, as well,

were significantly higher than those in the hippocampus which concentrated the lowest amount. Marked increases in the levels of unchanged DMPEA-14C were observed in almost all brain areas of rabbits pretreated with iproniazid. In animals pretreated with reserpine, the levels of total radioactivity and nondeaminated compounds were significantly increased in the superior colliculus and the thalamus. The high concentrations of DMPEA in some regions belonging to the extrapyramidal system may have significance in the DMPEA-induced akinesia. 36 references. (Author abstract modified)

113987 Schwartz, Morton A.; Kolis, Stanley J. Hoffmann-LaRoche Inc., Nutley, N.J. 07110 Pathways of medazepam metabolism in the dog and rat. *Journal of Pharmacology and Experimental Therapeutics.* 180(1):180-188, 1972.

The in vitro metabolism of medazepam to diazepam on incubation with 9000 X g supernatant of rat liver was investigated. This conversion was found to proceed via the formation of 2-hydroxymedazepam, which was dehydrogenated to diazepam. The latter reaction, oxidation of an alcohol, was unusual in that it was mediated primarily by an enzyme located in the microsomes rather than in the soluble fraction of rat liver. The dog liver 9000 X g supernatant did not form significant amounts of diazepam from medazepam because this dehydrogenation of 2-hydroxymedazepam was almost completely absent. Instead, N-demethylation of this intermediate was preferred. The in vivo metabolism of medazepam to 2-hydroxymedazepam and diazepam in the rat was consistent with that found in vitro. In the dog, however, the in vivo formation of a diazepam metabolite was observed. 15 references. (Author abstract)

113989 Thoa, Nguyen B.; Johnson, David G.; Kopin, Irwin J. Laboratory of Clinical Science, NIMH, Bldg 10, Room 2D-46, Bethesda, Md. 20014 Inhibition of norepinephrine biosynthesis by alpha-methyl amino acids in the guinea-pig vas deferens. *Journal of Pharmacology and Experimental Therapeutics.* 180(1):71-77, 1972.

In the isolated vas deferens of the guinea pig both alpha-methyl-m-tyrosine and alpha-methyldopa decreased formation of norepinephrine from tyrosine-14C. Inhibition was apparent even during the accelerated synthesis of norepinephrine produced by stimulation of the hypogastric nerves. Both drugs also decreased formation of norepinephrine and dopamine from labeled dopa. In organs treated with the dopa decarboxylase inhibitor NSD-1055, both alpha-methyl-m-tyrosine and alpha-methyldopa decreased the formation of dopa-14C from tyrosine-14C. alpha-Methyl-m-tyrosine inhibited the uptake of tyrosine-14C into the vas deferens, and alpha-methyldopa inhibited the uptake of labeled dopa. These results suggest that the alpha-methylated compounds can inhibit synthesis of norepinephrine in concentrations lower than those necessary to inhibit the enzymes involved in the biosynthesis of norepinephrine. This inhibition may be in part the result of interference with uptake of the labeled precursor amino acids into the sympathetic nerves. 21 references. (Author abstract)

113990 Ziance, Ronald J.; Sipes, I.Glenn; Kinnard, William J., Jr.; Buckley, Joseph P. Dept.of Pharmacology, Univ.of Georgia School of Pharmacy, Athens, Ga. 30601 Central nervous system effects of fenfluramine hydrochloride. *Journal of Pharmacology and Experimental Therapeutics.* 180(1):110-117, 1972.

Fenfluramine is a phenethylamine compound with a structure similar to that of amphetamine. These 2 structurally similar compounds possess several major differences in pharmacologic properties, especially with regard to their effects on the central nervous system. d-Amphetamine produced a dose related increase of spontaneous motor activity (SMA) in mice; however, dl-fenfluramine decreased the SMA in a dose related manner. Biochemical studies revealed that dl-fenfluramine decreased the content of norepinephrine and dopamine in mouse and rat brain. Pretreatment of mice with a monoamine oxidase inhibitor reversed the effect of dl-fenfluramine from one of significant decrease of SMA to one of a marked increase of SMA; however, the ability of d-amphetamine to increase SMA of mice was enhanced by prior monoamine oxidase inhibition. These data suggest that d-amphetamine and dl-fenfluramine differ in their interaction with central adrenergic neurons to produce their respective SMA effects in mice. 25 references. (Author abstract)

113991 Ziance, Ronald J.; Rutledge, Charles O. Dept.of Pharmacology, School of Pharmacy, Univ.of Georgia, Athens, Ga. 30601 A comparison of the effects of fenfluramine and amphetamine on

uptake, release and catabolism of norepinephrine in rat brain. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(1):118-126, 1972.**

The actions of amphetamine and fenfluramine on the uptake, release and catabolism of norepinephrine in rat cerebral cortex was examined. Fenfluramine and amphetamine both inhibit the accumulation of 3H-norepinephrine into rat brain cortex tissue slices but d-amphetamine is about 50 times more potent than either d-, l- or dl-fenfluramine. When 3H-norepinephrine is added to cortex slices in the presence of fenfluramine, oxidative deamination of 3H-norepinephrine is reduced markedly. When tissues are incubated with 3H-norepinephrine prior to exposure to the drugs, both fenfluramine and amphetamine release 3H-norepinephrine into the media; fenfluramine is again less potent than amphetamine. Under these conditions, fenfluramine increases the amount of 3H-deminated metabolites which are formed. This is in contrast to amphetamine. If the tissue is exposed to pargyline, a monoamine oxidase inhibitor, the amount of 3H-norepinephrine released into the media by fenfluramine is increased markedly when compared to the amount released by fenfluramine alone. After pargyline treatment, fenfluramine is equipotent with amphetamine. The effect of amphetamine on the release of norepinephrine is not increased significantly by treatment with pargyline. These results suggest that fenfluramine and amphetamine differ in the mechanism by which they release norepinephrine from brain tissue. Amphetamine releases unmetabolized norepinephrine, whereas fenfluramine releases norepinephrine in such a manner that it has increased access to monoamine oxidase. 35 references. (Author abstract modified)

113992 Morgan, C.D.; Cattabeni, F.; Costa, E. Laboratory of Preclinical Pharmacology, NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Methamphetamine, fenfluramine and their N-dealkylated metabolites: effect on monoamine concentrations in rat Methamphetamine, fenfluramine and their N-dealkylated metabolites: effect on monoamine concentrations in rat tissues. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(1):127-135, 1972.**

The sensitive technique of gas chromatography - mass spectrometry was used to detect and identify metabolites of methamphetamine and fenfluramine in rat tissue after i.p.administration of doses which cause tissue monoamine depletion. Methamphetamine causes a long-lasting depletion of heart norepinephrine and a shorter-lasting depletion of brain norepinephrine and 5-hydroxytryptamine, whereas fenfluramine produces a selective and long-lasting depletion of brain 5-hydroxytryptamine. After production of trimethylsilyl hepafluorobutyryl derivatives of these drugs and their metabolites, the technique of mass fragmentography facilitated the detection and identification of the N-dealkylated metabolites of methamphetamine, and amphetamine and p-hydroxyamphetamine in tissues. The N-dealkylated metabolite of fenfluramine, norfenfluramine, was similarly detected in tissue homogenates of rats killed up to 24 hours after injection. The N-dealkylation of both drugs involves a stereoisomeric dependence and gives rise to metabolites which persist in tissues and conceivably are involved in tissue monoamine depletion. 18 references. (Author abstract)

114040 Saad, S.F.; El Masry, A.M.; Scott, P.M. Department of Pharmacology, Faculty of Pharmacy, Kasr E Aini, Cairo, Egypt Influence of certain anticonvulsants on the concentration of gamma-aminobutyric acid in the cerebral hemispheres of mice. ***European Journal of Pharmacology (Amsterdam).*** **17(3):386-392, 1972.**

A study was made, in mice, of the effects of certain drugs of the barbiturate and hydantoin groups, used in the treatment of grand-mal epilepsy, on the gamma-aminobutyric acid (GABA) content of normal cerebral hemispheres and of cerebral hemispheres depleted of GABA. It was shown that: (1) i.p.administration of the sodium salts of phenobarbital, prominal, diphenlhydantoin and mesantoin increased cerebral hemisphere GABA content of mice; (2) the GABA content increased to a peak 1 hr after the administration of the sodium salts of prominal and mesantoin, 2 hr after phenobarbital and 3 hr after diphenylhydantoin and then returned to normal; (3) the sodium salts of phenobarbital, prominal, primidone, diphenlhydantoin and mesantoin significantly increased the cerebral hemisphere concentration of GABA, previously reduced by isoniazid, to normal concentrations and antagonized the convulsions produced by isoniazid. The present results suggest a probable mechanism, in terms of their effect on the cerebral hemisphere GABA content, by which these anticonvulsants produce their action. 19 references. (Author abstract)

114041 Rowland, Malcolm. University of California, School of Pharmacy, San Francisco, California 94122 Application of clearance concepts to some literature data on drug metabolism in the isolated perfused liver preparation and in vivo. ***European Journal of Pharmacology (Amsterdam).*** **17(3):352-356, 1972.**

Using the data of Von Bahr et al.the interrelationships between half-life, volume of distribution and clearance of a drug in vivo and in the isolated perfused liver were examined. Clearance measurements are the most meaningful when comparing the handling of drugs in the isolated perfused liver system to that in vivo. The application of clearance concepts to drug availability and enzyme induction studies are discussed. Phenylbutazone, antipyrine, oxotremorine, nortriptyline, and desmethylimipramine were the drugs investigated. 9 references. (Author abstract modified)

114042 Landmark, Knud. Institute of Pharmacology, University of Oslo, Blindern, Oslo 3, Norway The action of promazine and thioridazine in isolated rat atria. 3. Effects of varying concentrations of calcium and different frequencies and strengths of stimulation on contractile force and excitability. ***European Journal of Pharmacology (Amsterdam).*** **17(3):365-374, 1972.**

The effects of promazine and thioridazine on electrically stimulated left rat atria were studied in the presence of varying concentrations of calcium and at different frequencies and strengths of stimulation. An increase of the calcium concentration in the Ringer solution increased the force of contraction of the preparations. A slight decrease in excitability was found above 4.0meq/1calcium. Suprathreshold stimulation (50 mA) produced a considerable increase in contractile force when calcium was 2.0meq/1, but on increasing the calcium concentration, this augmentation declined rapidly. On the basis of experiments with an adrenergic beta-blocker, practolol, and atropine sulphate, it is concluded that suprathreshold stimulation releases noradrenaline as well as acetylcholine. The decrease in contractile force caused by promazine and thioridazine was, to a certain extent, antagonized by increasing the concentration of calcium ion. In atria stimulated at suprathreshold values, the results indicate that some sort of competition between calcium ion and the phenothiazine derivatives may exist, and it is assumed that the drugs interfere with the exchangeability of calcium available for contraction. The decrease in excitability caused by promazine seemed to be independent of varying calcium ion concentration. An increase in the frequency of contractions increased the threshold for electrical stimulation and reduced the contractile force ('negative staircase'). Promazine enhanced these effects. It is concluded that the degree of the phenothiazine induced reduction in contractile force of isolated rate atria depends upon the calcium concentration of the Ringer solution and also on the frequency and strenth of stimulation. 57 references. (Author abstract)

114064 Kasirsky, G.; Zaidi, I.H.; Tansy, M.F. Dept.of Pharmacology, Kansas City College of Osteopathic Medicine, Kansas City, Mo. 64124 LD50 and pathologic effects of acute and chronic administration of methamphetamine HCl in rabbits. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):215-231, 1972.**

LD50 and the pathologic effects of acute and chronic administration of methamphetamine hydrochloride were studied in rabbits. In New Zealand white rabbits 1 dose oral and intravenous and 90 dose oral LD50 values for methamphetamine HCl were determined to be 10.5(7.7-11.9)mg/kg and 3.0(2.7- 3.8)mg/kg and 55(45 - 65) mg/kg respectively. The chronicity factor was 5.2. At the end of a 120 day period, 29 of 50 rabbits exposed to 300mg/day of methamphetamine HCl survived. A new i.v.LD50 was determined to be 26(22 - 33)mg/kg. The clinical signs of acute i.v.poisoning were recorded. Gross and microscopic post mortem examinations revealed subendocardial petechial hemorrhages, neuronal ganglion cell degeneration with encephalomalacia and marked pallor of the brain. Ecchymotic and petechial hemorrhages of the thymus and lungs were also observed. Microscopic examination revealed centrolobular congestion and fatty degeneration of the liver parenchymal cells together with degenerative changes in the renal tublar epithelium and coagulation necrosis. Acute suppurative bronchopneumonia with pulmonary edema and congestion was also observed. Hematology examination revealed thrombocytopenia and increased prothrombin time. 32 references. (Author abstract modified)

114065 Plotnikoff, N.; Fedor, E.J. General Pharmacology Dept., Abbott Laboratories, North Chicago, Ill. 60064 Pemoline; cardiovascular studies. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):233-243, 1972.**

Cardiovascular studies of pemoline in the dog are reported. Pemoline and Mg(OH)2 (PMH), a mild stimulant has been reported to enhance learning and to antagonize amnesia. No alterations in cardiovascular function were produced by oral administration of PMH, 5mg/kg, in the unanesthetized dog. Doses as high as 25mg/kg, orally, in the unanesthetized dog did not consistently affect arterial blood pressure, heart rate, the electrocardiogram, mean aortic blood flow, or calculated cardiac work. These results are significantly different from those seen with sympathomimetic agents that produce central nervous system stimulation. PMH did not seem to affect autonomic function. 7 references. (Author abstract modified)

114066 Everett, G.M.; Borcherding, J.; Morse, P. Dept.of Pharmacology, Univ.of California School of Medicine, San Francisco, Calif. 94122 Effect of deserpidine and pargyline on the levels of biogenic amines in brain, liver and heart of mice. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):245-248, 1972.**

Dopamine, norepinephrine and serotonin levels were determined in mouse brain, liver, heart and spleen. Dopamine is highest in brain and serotonin highest in spleen. In drug studies with deserpidine and pargyline, brain and heart show similar effects while amine levels in liver were much less affected by these drugs. 3 references. (Author abstract)

114067 Weiner, Myron; Buterbaugh, Gary G.; Blake, David A. Dept.of Pharmacology, Univ.of Southern California School of Pharmacy, Los Angeles, Calif. 90007 Inhibition of hepatic drug metabolism by cyclic 3',5'-adenosine monophosphate. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):249-263, 1972.**

The inhibition of hepatic drug metabolism by cyclic 3',5'-adenosine monophosphate (cAMP) is reported. Starvation (72 hrs), alloxan diabetes (72 hr pretreatment), or glucagon (48 and 24 hr pretreatment) caused an increase in hexobarbital sodium (HB) sleeping time without altering brain sensitivity to the barbiturate in male rats. This increase in sleeping time could be markedly antagonized by insulin (48 and 24 hr pretreatment). cAMP involvement in glucagon's effect was implied when combined glucagon and theophylline pretreatments caused an increase in the duration of HB hypnosis at doses (glucagon, 10mg/kg; theophylline, 100mg/kg i.p.,25 min pretreatment) which separately had no effect. Direct support for the involvement of the cyclic nucleotide was the ability of dibutyryl cyclic AMP (DBcAMP) to increase HB sleeping time. The effect of DBcAMP was rapid in onset (10 min) and long lasting (over 24 hrs). The glucagon and theophylline combination inhibited the rate of HB disappearance in the isolated, perfused rat liver; in addition, DBcAMP inhibited HB and p-chloro-N-methylaniline metabolism. Therefore, the inhibition of drug metabolism by the cyclic nucleotide is mediated in the liver. 25 references. (Author abstract modified)

114069 Friedhoff, A.J.; Schweitzer, J.W.; Miller, Jeannette. Millhauser Laboratories of the Dept.of Psychiatry, New York Univ.School of Medicine, 550 First Ave., New York, N.Y. 10016 The enzymatic formation of 3,4-di-O-methylated dopamine metabolites by mammalian tissues. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):293-311, 1972.**

In a series of experiments it was demonstrated that a dopamine metabolite, N-acetyl-3-hydroxy-4-methoxyphenethylamine, (i-NAMT) can be transformed enzymatically to N-acetyl-3, 4-dimethoxy phenethylamine (NADMPEA) by mamalian tissues. It can be concluded, therefore, that a 3, 4-dimethoxy derivative of a catechol structure is a possible product of catecholamine metabolism. 16 references. (Author abstract)

114070 Sankar, D.V.Siva. Queens Children's Hospital, Bellerose, New York 11426 Interrelations of endocrine function and LSD-25: effect of psychoactive drugs and of removal of endocrine glands on oxygen uptake in the rat. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):321-338, 1972.**

The relation of psychoactive drugs to endocrine function was studied in the rat. The administration of LSD-25 to intact or to adrenalectomized rats increases their oxygen consumption, while it decreases it in thyroidectomized or hypophysectomized rats. Chlorpromazine decreases the oxygen consumption in all these animals. An excitant, namely JB 516, decreases oxygen consumption in intact and thyroidectomized animals. In intact rats, administration of LSD-25 within 75 minutes of the administration of thyrotropic hormone, also causes reduction in oxygen consumption. Some of the effects of LSD-25 are possibly

mediated from the thyroid. In rats with lesions in the hypothalamus, the effects of LSD-25 and of chlorpromazine are not as pronounced. This may indicate the centrally mediated action of these 2 psychotropic drugs. By clinical extrapolation these studies show the variability and danger of both use and abuse of psychotropic drugs in human endocrinopathies. This is all the more relevant in the use of sympathomimetics in cases of thyroid dysfunction and thyrotropic medication. A target site for LSD-25 is TSH. 22 references. (Author abstract modified)

114093 Cox, Raymond H., Jr.; Maickel, Roger P. Mead Johnson Research Center, Evansville, Ind. 47721 Comparison of anorexigenic and behavioral potency of phenylethylamines. ***Journal of Pharmacology and Experimental Therapeutics.*** **181(1):1-9, 1972.**

A number of compounds containing a phenylethylamine structure were tested in rats to determine the potency of their anorexigenic effects (as measured by depression of hunger induced food intake) and of their behavioral effects (as measured by effects on continuous avoidance responding). All of the compounds tested were effective in reducing the food intake of hungry rats. The most potent compounds were fenfluramine and p-chloroamphetamine, with molar potencies one third greater than that of d-amphetamine, whereas the least potent compound was p-hydroxyamphetamine with a molar potency less than 6% that of d-amphetamine. In the behavioral tests, the compounds fell into 3 classes, either increasing, decreasing or having no effect on the rate of avoidance responding. The majority of the compounds acted as stimulants to increase the rate of avoidance responding, with the most potent one, methamphetamine, having a molar potency 3 times that of amphetamine. The least potent stimulant compound was phendimetrazine, with a molar potency approximately 0.1that of amphetamine. Fenfluramine, p-methylamphetamine and p-chlorobenzphetamine were depressant in action , whereas chlorphentermine, benzphetamine and p-hydroxyamphetamine had no significant effects on avoidance responding. 18 references. (Author abstract)

114522 Russek, M.; Stevenson, J.A.F. Escuela Nacional de Ciencias Biologicas, Instituto Politecnico Nacional, Mexico, 17 D.F.Mexico Correlation between the effects of several substances on food intake and on the hepatic concentration of reducing sugars. ***Physiology & Behavior.*** **8(2):245-249, 1972.**

A study was made of the correlation between the effects of several substances on food intake and on the hepatic concentration of reducing sugars. Food intake, and concentration of reducing sugars in blood, liver, muscle and adipose tissue were determined after intraperitoneal injections of: adrenaline, noradrenaline, glucose, insulin and amphetamine. Excluding amphetamine, the changes in liver sugar concentration, measured in 23 hr fasted or nonfasted rats, showed a significant inverse correlation with the changes in food intake of rats eating for 1 hr daily while those of muscle and adipose tissue did not.The blood glucose of fasted rats did not show any correlation with the changes in food intake. On the other hand, amphetamine produced a smaller increase in liver reducing sugars than that expected from the above correlation and no increase in blood sugar, but elicited a reduction of liver glycogen similar to that produced by the isoanorexigenic dose of adrenaline. Moreover, the anorexigenic effects of both adrenaline and amphetamine decreased significantly in rats with reduced liver glycogen. These observations appear to support the hypothesis that liver glucoreceptors play an important role in the control of food intake. The results of amphetamine suggest that stimulus for these receptors may not be the actual glucose concentration, but the rate of glucose change. A decreasing glucose concentration in the liver cells would produce hunger signals, while an increasing concentration would stop these signals. 14 references. (Author abstract modified)

114562 Morgane, Peter J.; Stern, Warren C.; Bronzino, Joseph D. Worcester Foundation for Experimental Biology Effects of centrally administered carbachol on sleep in cats. ***Psychophysiology.*** **9(1):86, 1972.**

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that in order to delineate chemospecific neurobehavioral systems in the brain concerned with sleep states, exploring chemitrode devices were implanted in cats wired for recording the usual sleep indicators. Since cholinergic stimulation within the medial forebrain bundle (MFB) was previously shown to induce sleep in over a hundred loci along its trajectory, it was decided to reexplore this system and quantify the effects of direct cholinergic stimulation on

specific sleep states. Cholinergic stimulation produced significant increases in REM time in 5 hypothalamic and preoptic loci, with REM sleep increasing from 14 to 33% of total recording time in 8 hour recording sessions following stimulation. Insignificant effects were produced on slow-wave sleep. These data confirm the existence of cholinoceptive sleep sites in the MFB and indicate that this heterogeneously organized neural pathway must be considered, in regard to the sleep states, to contain not only subsystems which regulate noradrenaline and serotonin, but possibly those which may regulate acetylcholine levels in its basal forebrain fields of projection. It is also possible that cholinergic synapses exist in the noradrenergic or serotonergic pathways and that these systems are activated by cholinergic stimulation, thus resulting in changes in the sleep state. (Journal abstract modified)

114565 Rodden, Appletree; Zarcone, Vince; DeGrazia, Joseph; Sinha, Arabinda; Barchas, Jack; Dement, William. Stanford University School of Medicine An effect of sleep on the in vivo rate of tryptophal decarboxylation. *Psychophysiology.* 9(1):85, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is noted that when an amino acid labeled with 14C02 in the carboxyl position is injected into the animal body, 14C02 soon appears in the breath. Its rate of appearance depends on the amino acid employed and the metabolic state of the organism. Since decarboxylation is 1 step leading from amino acids to biogenic amines, the rate of 14C02 expiration from subjects injected with 1-14C-amino acids during wakefulness and sleep was measured. On 1 night, the subject lay awake with his head in a collection hood and at midnight, the amino acid (20 microCi) was injected via an indwelling catheter previously placed in the subject's arm. On the other night, EEG electrodes were attached, the indwelling catheter placed in his arm, and the subject allowed to sleep. When the EEG showed that he was asleep, a bolus of the amino acid (20 microCi) was delivered without waking him. On both nights, the specific activity of the expired 14C02 was continuously measured for 5 hours after the injection. The rate of 14C02 expiration from sleeping subjects injected with tryptophal was markedly slower than that of the awake subjects. Only much smaller changes were seen when tyrosine or histidine were studied. (Journal abstract modified)

114568 Stern, Warren C.; Morgane, Peter J. Worcester Foundation for Experimental Biology Effects of catecholamine modulating drugs on sleep in the cat. *Psychophysiology.* 9(1):86, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which 2 catecholamine (CA) antagonists (DL-alphamethylparatyrosine (AMPT)) or AMPT methyl ester at 75mg/kg and reserpine at 0.15mg/kg and 2 CA potentiators (imipramine at 4mg/kg and DL-dopa given in 2 injections at 30 and 15mg/kg plus vitamin B6) were administered intraperitoneally to assess the role of brain CA in producing REM sleep. Polygraph recordings from freely moving, chronically implanted cats showed that AMPT and AMPT methyl ester selectively increased REM sleep to 150 to 200% of baseline during the period of 3 to 7 hours after injection. Reserpine, on the other hand, decreased REM and slow-wave sleep for several days. The effect of reserpine on REM was partially reversed by administering DL-dopa. This effect is not necessarily due to enhanced CA since dopa given after reserpine has been reported to increase acetylcholine, and enhanced cholinergic activity following reserpine has been reported to reverse the reserpine induced reduction of REM. Both imipramine and dopa lowered REM by 70%. Imipramine did not reduce slow-wave sleep while dopa mainly produced an increase in arousal. These results support the view that REM sleep maintains CA systems since decreases in brain CA (by AMPT) produced a (compensatory) increase in REM, while enhanced brain CA (by imipramine) selectively lowered REM time. (Journal abstract modified)

114569 Clarenbach, Peter; Welter, Mathias; Cramer, Hinrich. University of Freiburg, Germany Influence of a chemical sympathectomy and of norepinephrine on the polygraphic sleep pattern of young chicks. *Psychophysiology.* 9(1):86, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is noted that noreprinephrine (NE) provokes a sleep like state if applied in small dosage systematically to young chicks or intracerebrally to adult fowl. Polygraphic recordings of night sleep were performed on 4 to 9 day old

chicks to study the influence of NE. REM sleep was found to be 9% of total sleep, the average duration of REM phases being less than 6 sec, in agreement with earlier findings. NE (3.74 micromoles/kg i.p.)initially decreased slightly and after 30 min significantly increased the percentage of REM sleep. In chicks chemically sympathectomized by repeated injection of 6-hydroxydopamine on the second to fifth day of life, the percentage of REM sleep was decreased. In sympathectomized chicks there was an earlier and more pronounced increase of REM sleep after injection of NE than in intact animals. The results suggest that the decrease in REM sleep is due to the loss of endogenous cathecholamines, and that postsynaptic adrenergic sites remain responsive to exogenous NE after treatment with 6-hydroxydopamine and seem to present denervation sypersensitivity. (Journal abstract modified)

114570 Bauman, Sherry; Henriksen, Steven; Barchas, Jack; Dement, William. Stanford Univeristy, Stanford, California Intraventricular 6-hydroxydopamine and sleep patterns in the rat. ***Psychophysiology.*** **9(1):86-87, 1972.**

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that stainless steel cannulae were implanted into the lateral ventricle of 9 male Wistar rats and 5 were also implanted for sleep recordings. The latter 5 animals were recorded during a standard 4 hour interval within the light portion of the day and a standard 3 hour interval within the dark portion for 8 consecutive days. On day 4, 2 hours prior to the first recording session, 4 of the 5 animals received 200 micrograms of 6-hydroxydopamine (in 25 microliters saline with 1mg/ml ascorbic acid added) via the cannulae and the 5th received 25 microliters saline with ascorbic acid only. At the same time, the 4 rats with cannulae only were injected, 2 with 6-hydroxydopamine and 2 with vehicle only. Immediately following the 8th recording day, the brains of all animals were analyzed for amine levels. There was no significant change in NREM sleep from the baseline mean (days 1 to 2) on any of the postinjection days (4 to 8). In all 4 rats receiving 6-hydroxydopamine, REM sleep was at 0 on day 4 (first postinjection day). On day 5, all rats began to show REM sleep, and by day 8, all were at or near the baseline level. No REM reduction at all was seen in the rat which received ascorbic acid only. The biochemical data showed norepinephrine (NE) at approximately 40% of controls and dopamine at 80%. There were no group differences in serotonin levels. These data fail to support the notion that NE and dopamine in the telencephalon and diencephalon are crucial for the occurrence of normal amounts of REM sleep in the rat within the range of depletion reported above. (Journal abstract modified)

114576 Anden, Nils-Erik; Corrodi, Hans; Fuxe, Kjell. Dept.of Pharmacology, Univ.of Goteborg, Goteborg, Sweden Effect of neuroleptic drugs on central catecholamine turnover assessed using tyrosine- and dopamine-beta-hydroxylase inhibitors. ***Journal of Pharmacy and Pharmacology (London).*** **24(3): 177-182, 1972.**

The effects of some neuroleptic drugs on the noradrenaline turnover in the rat brain and spinal cord were studied biochemically and histochemically with the help of a new inhibitor of the enzyme dopamine-beta-hydroxylase, bis(4-methyl-1-homopiperazinyl-thiocarbonyl) disulphide; (FLA-63). Haloperidol, chlorpromazine, pimozide and fluspirilene produced an acceleration of the noradrenaline disapperance induced by FLA-63. Clothiapine was ineffective. The lowering of brain dopamine after treatment with alpha-methyltyrosine methylester was markedly enhanced by haloperidol and slightly so by chlorpromazine, whereas both drugs simultaneously caused a significant increase in the noradrenaline loss. Thus, the same results were obtained with dopamine-beta-hydroxylase and tyrosine-hydroxylase inhibition on the influence of neuroleptic drugs on the noradrenaline turnover. The acceleration seen after haloperidol and chlorpromazine, but not after pimozide and fluspirilene, could be due to a compensatory activation of noradrenaline neurons produced by a noradrenaline receptor blockade. 26 references. (Author abstract modified)

114581 Tacker, Martha; McIsaac, W.M.; Creaven, P.J. Dept.of Physiology, Baylor College of Medicine, Houston, Tex. 77025 Effect of tranylcypromine sulphate on the metabolism of (14C)tyramine in vivo in the rat. ***Journal of Pharmacy and Pharmacology (London).*** **24(3):245-246, 1972.**

The effect of tryanylcypromine sulphate on the metabolism of (14C)tyramine was studied in vivo in the rat. Pretreatment with tranylcypromine decreased the oxidative metabolism of tyramine and increased the production of nonoxidative

metabolites. In another test, essentially the same results were obtained with pargyline hydrochloride. In both studies, unidentified metabolite were excreted by rats. 10 references.

114625 Planz, G.; Quiring, K.; Palm, D. Pharmakologisches Institut der Universita, D-6000 Frankfurt a.M.70, Ludwig Rehn-Strasse 14, Germany Rates of recovery of irreversibly inhibited monoamine oxidases: a measure of enzyme protein turnover. *Archives of Pharmacology.* 273(1/2):27-42, 1972.

After irreversible inhibition of monoamine oxidase (MAO) in rats with hydrazine derivatives (3-amino-2-oxazolidinone, furazolidone, benmoxine) and the nonhydrazine pargyline, recovery of enzyme activity occured at rates which were characteristic for the organ investigated and independent of the chemcial structure of the irreversible inhibitor. The respective half times were the same in homogenates and in mitochondria and amounted to about 10 days in the brain and 3 to 4 days in the liver; in the small intestine, mucosal MAO activity recovered with a half time of 0.5days, whereas in the residual intestinal layers a half time of about 4 days was found. Tranylcypromine is not an irreversible inhibitor: the half times of MAO recovery were 3.6days in the brain and 2.4days in the liver. When mitochondrial protein was labelled by i.v. injection of 14C-leucine, specific radioactivity declined with a half time of 9.4days in the brain and 4.0days in the liver; for the intestinal mucosa and for the residual intestinal layers, a half time of 0.5and 4.4days, respectively, was found. As these values are nearly identical with those found for the rates of MAO recovery after irreversible inhibition, the assumption is supported that irreversibly inhibited MAO must be replaced by newly synthetized enzyme. Vice versa, the rates of MAO recovery after irreversible inhibition seem to reflect the rates of mitochondrial protein turnover. Measurements of the rate of recovery of irreversibly inhibited MAO activity may therefore be useful to determine the turnover of the enzyme protein. 40 references. (Author abstract)

114626 Meisch, Jean-Jacques; Waldeck, Bertil. Netherlands Central Institute for Brain Research, Amsterdam, The Netherlands On the disposition of 4,alpha-dimethylmetatyramine in the brain and heart of the mouse. *Archives of Pharmacology.* 273(1/2):75-85, 1972.

4-alpha-Dimethylmetatyramine (H 77/77) and 4-methylmetaraminol (H 65/45) were given to mice intraperitoneally. At various time intervals the animals were killed and the amines were determined in brain and heart. Both amines were equally taken up by the heart and then disappeared biphasically. In the brain, the uptake of H 77/77 and H 65/45 was delayed as compared with the heart and the amines disappeared single - exponentially with a half life of about 1.5h which was the same as for the second, slow phase in the heart. The 2 amines differed in that the beta-hydroxyl derivative, H 65/45 was less efficiently taken up in the brain than was H 77/77. The uptake of H 77/77 showed no signs of saturation at a dose of 25mg/kg. An in vivo conversion of H 77/77 to H 65/45 could not be demonstrated. Experiments with protriptyline and reserpine indicate that, apart from the early phase in the heart, H 77/77 is located mainly intraneuronally. The poor affinity for the enzyme dopamine beta-hydroxylase and for the granular storage mechanism of the adrenergic neuron might be due to the 4-methyl group on the ring. 19 references. (Author abstract modified)

114643 Bhargava, K.P.; Rastogi, S.K.; Sinha, J.N. Dept.of Pharmacology and Therapeutics, King George's Medical College, Lucknow-3, India The muscle relaxant activity of methaqualone and its methyl congener. *British Journal of Pharmacology (London).* 44(4):805-806, 1972.

The muscle relaxant activity of methaqualone and its methyl congener was studied in rabbits and cats. It was shown that methaqualone and dimethylquinazolone showed them to possess both central and peripheral muscle relaxant activity, the latter only at high dose levels. They selectively inhibited polysynaptic reflexes and were more potent than mephenesin. 6 references. (Author abstract modified)

114644 Bustos, G.; Roth, R.H. Dept.of Pharmacology, Yale Univ.School of Medicine, New Haven, CT Effect of gamma-hydroxybutyrate on the release of monoamines from the rat striatum. *British Journal of Pharmacology (London).* 44(4):817-820, 1972.

A simple in vitro system was developed to study the effect of gamma-hydroxybutyrate on nerve cell depolarization induced release of labelled dopamine (DA) and 5-hydroxytryptamine (5-HT). The release of 3H-dopamine formed in rat

striatal slices incubated with 3H-tyrosine was followed. A 3 minute exposure to K ion caused an increase in the release of newly synthesized 3H-dopamine. This K ion induced release was antagonized when gamma-hydroxybutyrate was present in the medium. Potassium increased the release of 3H -dopamine from striatal slices initially loaded by preincubation with 3H-dopamine. The K ion induced release of this pool of DA was, however, not antagonized by gamma-hydroxybutyrate. Potassium also increased the release from striatal slices of 3H-5-hydroxytryptamine newly synthesized from 3H-tryptophan. This K ion induced release of 5-HT was also not inhibited by gamma-hydroxybutyrate to antagonize only the K gamma induced release of newly formed DA may explain why this agent causes a rapid and selective increase in brain dopamine. 15 references. (Author abstract modified)

114687 Leonard, B.E.; Stonier, P.D. Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England Some neurochemical and neuropharmacological studies on the interactions between mescaline and 1-methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboxamid de) (THPC). ***Psychopharmacologia (Berlin).*** **25(1):1-13, 1972.**

The effect of 1-methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboxamide) (THPC) was studied on some pharmacological and neurochemical changes induced in the rat by mescaline. THPC antagonized the effect of mescaline on the calorigenic action of 4-alpha-methyl-m-tyrosine in reserpinized mice. THPC potentiated the depletion of brain dopamine caused by 4-alpha-dimethyl-m-tyramine in combination with mescaline. In none of the other pharmacological or neurochemical tests was there any evidence that THPC antagonized or potentiated the effects of mescaline. 20 references. (Author abstract modified)

114734 Frisk-Holmberg, Marianne; van der Kleijn, Eppo. Dept.of Pharmacology, Karolinska Institutet, Stockholm, Sweden The relationship between the lipophilic nature of tricyclic neuroleptics and antidepressants, and histamine release. ***European Journal of Pharmacology (Amsterdam).*** **18(2):139-147, 1972.**

The relative histamine releasing activity of tricyclic psychoactive drugs, using rat mast cells, was determined. The presence of a halogen or a halogen containing group at position 2 in the neuroleptics or at position 3 in the antidepressants, and/or carbon instead of nitrogen at position 10 in the neuroleptics or at position 5 in the antidepressants and an unsaturated bond in the aliphatic sidechain increased histamine releasing activity when compared with unsubstituted homologues. The presence of a piperidine or piperazine ring in the sidechain increased histamine releasing activity. From these substituted compounds, those having a methyl group at the terminal nitrogen were more active than homologues with an alcohol group at the nitrogen. For antidepressants, aliphatic tertiary amines were more active than secondary amines. Lipophilic nature was expressed as the partition coefficients of the drugs in a octanol -- buffer and chloroform -- buffer system. A significant correlation was found, between lipophilic nature and histamine releasing activity. 22 references. (Author abstract modified)

114870 Lieber, Charles S.; DeCarli, Leonore M. Section of Liver Disease and Nutrition, VA Hospital, 130 West Kingsbridge Road, Bronx, NY 10468 The role of the hepatic microsomal ethanol oxidizing system (MEOS) for ethanol metabolism in vivo. ***Journal of Pharmacology and Experimental Therapeutics.*** **181(2):279-287, 1972.**

To assess the in vivo role of the microsomal ethanol oxidizing system (MEOS), an improved assay procedure was developed. When corrected for losses of microsomes during the preparation, the activity of MEOS in vitro corresponded to 20 to 25% of the in vivo rate of ethanol metabolism in the rat and could account for most of the residual ethanol metabolism after inhibition of alcohol dehydrogenase by pyrazole. Under these conditions, the apparent Km of MEOS in vitro coincided with the apparent Km of the blood ethanol disappearance in vivo. Furthermore, administration of ethanol to rats for 24 days increased blood ethanol clearance, with a parallel rise in MEOS activity, whereas the activities of alcohol dehydrogenase and catalase remainded unchanged or decreased. Moreover, barbiturate treatment for four to five days also increased total MEOS activity in the liver and this was accompanied by a moderate acceleration of blood ethanol clearance. The latter effect was masked if significant amounts of barbiturates were still present in the blood when ethanol was given. In addition, administration of one dose of barbiturate slowed blood ethanol clearance and abolished its

increase induced by ethanol pretreatment, suggesting that barbiturates interfere with the metabolism of ethanol. In view of the parallel increase of blood ethanol clearance in vivo and MEOS activity in vitro after ethanol or barbiturate pretreatment, it is proposed that MEOS plays a significant role in vivo, a conclusion supported by the correspondence of the kinetic data of MEOS in vitro and of blood ethanol clearance after alcohol dehydrogenase inhibition in vivo. 37 references. (Journal abstract)

114871 Wakade, Arun R.; Krusz, John. Downstate Medical Center, Department of Pharmacology, 450 Clarkson Avenue, Brooklyn, NY 11203 Effect of reserpine, phenoxybenzamine and cocaine on neuromuscular transmission in the vas deferens of the guinea pig. ***Journal of Pharmacology and Experimental Therapeutics.*** **181(2):310-317, 1972.**

The effects of reserpine, phenoxybenzamine and cocaine on neuromuscular transmission in the vas deferens of the guinea pig are presented. Chemical analysis of vasa deferentia taken from guinea pigs pretreated with high doses of reserpine showed almost complete depletion of their norepinephrine stores. However, the contractile response of the reserpine pretreated vas deferens to hypogastric nerve stimulation was still maintained at 60%of the control level. In vitro treatment with reserpine had no inhibitory effect on neuromuscular transmission in the vas deferens. Phenoxybenzamine was found to be ineffective in blocking nerve mediated responses of the vas deferens obtained from reserpine pretreated guinea pigs. In fact, phenoxybenzamine markedly potentiated (about fivefold) nerve mediated responses and, in addition, always induced spontaneous contractions of the reserpine pretreated vas deferens. In the presence of cocaine, contractions of the reserpine pretreated vas deferens induced by hypogastric nerve stimulation remained totally unaffected, whereas responses to exogenous norepinephrine were augmented nearly 300 fold. 24 references. (Journal abstract)

114979 Izquierdo, J.A.; Jofre, Isabel J.; Acevedo, Cristina. Catedra de Farmacologia Experimental, Facultad de Farmacia y Bioquimica, Junin 956, Buenos Aires, Argentina Effect of disulfiram and ascorbic acid on catecholamine content in rat brain. ***Journal of Pharmacy and Pharmacology (London).*** **24(4):330-332, 1972.**

The interaction between disulfiram which is an inhibitor of dopamine-beta-hydroxylase (DBH), and ascorbic acid 24, 48, and 72h after injection of disulfiram was studied in the rat brain. The dopamine and noradrenaline content of cortex, cerebellum, diencephalon, mesencephalon, and pons -medulla oblongata was measured. Disulfiram increased dopamine and decreased noradrenaline content after 2h, the effect being maximal after 4h. These responses were increased by ascorbic acid, though not significantly in the cerebral structures studied. Only in animals given disulfiram 72h before death did ascorbic acid produce a significant increase of noradrenaline in all the cerebral structures. Two main points are: the inhibitory effect of disulfiram on DBH in rat brain persists for 72h and ascorbic acid, per se, as cofactor, participates either in activating the hydroxylating enzyme, or counteracting an endogenous inhibitor of DBH. 14 references.

115038 Pluchino, S. Dept.of Pharmacology, School of Pharmacy, Central Univ.of Venezuela, Apartado 40.252-Nueva Granada, Caracas, Venezuela Direct and indirect effects of 5-hydroxytryptamine and tyramine on smooth cat muscle. ***Archives of Pharmacology (Berlin).*** **272(2):189-224, 1972.**

The effect of 5-hydroxytryptamine (5-HT) was studied on the nictitating membrane (isolated, or in situ in the pithed cat) and on strips of spleen capsule of the cat. On the nictitating membrane 5-HT (in low concentrations) has a direct effect on tryptamine receptors as well as (in high concentrations) an indirect effect which involves uptake of 5-HT into the adrenergic neuron via the cocaine sensitive mechanism and release of noradrenaline. On splenic strips 5-HT has a predominantly indirect effect. The direct effects of 5-HT on the nictitating membrane are not increased by denervation (2 days), cocaine or block of monoamine oxidase (MAO), while decentralization (14 days) leads to supersensitivity to this amine. The direct effects of 5-HT are resistant to phenotolamine; the indirect effects are increased by block of MAO. This potentiation is probably due to prevention of deamination of both the 5-HT and the released noradrenaline. The indirect effects of 5-HT are very similar to those of tyramine, and cross tachphylaxis was observed. Saturation of the tryptamine receptors of the nicitating membrane leads to desensitization. In addition, 5-HT antagonizes the effects of

noradrenaline on the alpha receptors. 45 references. (Author abstract modified)

115040 Sabelli, Hector C.; Giardina, William J. Dept.of Pharmacology, The Chicago Medical School, Chicago, IL Tranquilizing and electrophysiological effects of nicotine. ***Biological Psychiatry.*** **4(2):105-130, 1972.**

The effects of intravenous nicotine upon the spontaneous EEG, ipsilateral and contralateral responses evoked by direct stimulation of the anterior and posterior motor cortex, and optic cortex potentials evoked by flash stimuli, were studied in nonanesthetized rabbits. Nicotine differentially affected ipsilateral and contralateral direct evoked responses. It induced diphasic effects on both direct and visual evoked responses probably resulting from its diphasic effect on cholinergic receptors. The inhibitors of catecholamine metabolism, alpha-methyl-para-tyrosine, alpha-methyl-dopa, tetraethylthiuram disulfide, and pargyline, markedly modified the effects of nicotine on the visual evoked potentials (demonstrating their dependence upon endogenous catecholamine levels) and reduced nicotine induced depression of mouse exploratory behavior. Nicotine prolonged babiturate sleep in mice and reinduced sleep after recovery from anesthesia. Nicotine induced barbiturate potentiation and EEG arousal were not blocked by atropinic drugs. The central nervous system effects of nicotine appear to result from the activation of specific nicotinic cholinergic receptors and to be partially dependent on endogenous catecholaminic mechanism. 43 references. (Author abstract modified)

115067 Breyer, U. Institut fur Toxikologie der Universitat Tubingen, D-7400 Tubingen, Wilhelmstr.56, Germany Perazine, chlorpromazine and imipramine as inducers of microsomal drug metabolism. ***Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin).*** **272(3):277-288, 1972.**

Male rats were treated orally for seven days with perazine, chlorpromiazine, imipramine or phenobarbital; isolated liver microsomes were tested for their metabolic activities towards perazine, ethylmorphine and aniline. N-Demethylation of perazine and ethylmorphine was increased by all pretreatments. Aromatic hydroxylation of perazine was decreased in microsomes from pretreated animals, whereas aniline hydroxylation was enhanced even more by perazine and imipramine than by phenobarbital. The yield of perazine sulfoxide was increased by phenobarbital treatment only. Perazine N-oxide formation was reduced by treatment with psychoactive drugs to 75-90% of control values and by phenobarbital to less than 50% . The microsomal cytochrome P-450 concentration was slightly elevated by perazine and substantially by chlorpromazine and imipramine treatment. The tricyclic drugs investigated are potent inducers of the drug metabolizing enzyme system, the induction pattern differing in some respects from that seen after phenobarbital. 27 references. (Author abstract)

115072 Karobath, Manfred; Baldessarini, Ross J. Psychiatrische Universitatsklinik, University of Vienna, Austria Formation of catechol compounds from phenylalanine and tyrosine with isolated nerve endings. ***Nature New Biology (London).*** **236(68):206-208, 1972.**

Synthesis of catecholamines was studied in isolated nerve endings (synaptosomes) prepared from rat, mouse, guinea-pig, cat, and monkey brains. This approach permits study of hydroxylase activity in isolated neuronal tissue from the brain and utilizes only natural endogenous cofactor; it was used to compare ratios of formation of catechols from phenylalanine and tyrosine. The rate of hydroxylation of phenylalanine in nerve endings may be as great or even greater than that of tyrosine. The properties of the endogenous cofactors in isolated nerve endings resemble those of tetrahydrobiopterin. It is suggested that phenylalanine can act as a substrate for tyrosine hydroxylase in partially isolated nerv e endings from amine rich tissues of mammalain brian. This system has the advantage of operating without an added exogenous pteridine cofactor and it reflects physiological activity of the natural endogenous cofactor. 17 references.

115082 Fabre, Louis F., Jr.; Farmer, Robert W.; Pellizzari, Edo D.; Farrell, Gordon. Section of Neuroendocrinology, Texas Research Institute of Mental Sciences, Houston, TX 77025 Aldosterone secretion in pentobarbital-anesthetized ethanol-infused dogs. ***Quarterly Journal of Studies on Alcohol.*** **33(2):476-484, 1972.**

Experiments with male dogs showed that mean aldosterone and hydrocortisone secretion rates were similar in a control group and a group receiving 24ml of ethanol. Animals receiving 48ml

of ethanol exhibited an approximate 50%decrease in aldosterone secretory rates although hydro-cortisone secretory rates were unaltered. 23 references.

115173 Gogolak, G.; Krijzer, F.; Stumpf, Ch. Lehrkanzel fur Neuropharmakologie der Universitat Wien, A-1090 Wien, Wahringerstrasse 13a, Austria Action of central depressant drugs on the electrocerebellogram of the rabbit. *Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin).* 272(4):378-386, 1972.

The action of central depressant drugs (CDD) was investigated on the electrical activity of the cerebellum (CB) and/or red nucleus (RN) of the rabbit. They were divided into different groups according to their effect on the cerebello - rubral system: 1) classical hypnotics (barbiturates, paraldehyde, chloral hydrate, piperidinedione derivatives, methaqualone, ethinamate, bromvalurea), tranquilizers (benzodiazepine derivatives, meprobamate) and one volatile anesthetic agent (methoxyflurane) regularize the spontaneous activity of the CB and RN. The frequency of the drug induced rhythm depends on the depth of anesthesia. 2) Diethyl ether, urethane, ethyl alcohol and halothane do not regularize the electrical activities in the CB and RN; rather they desynchronize the spontaneous activity of these brain areas. 3) Trichlorethylene induces a high frequency and high amplitude rhythm in both the CB and RN during deep anesthesia. 4) With all CDD tested the drug induced CB rhythm is identical with the RN rhythm. 18 references. (Author abstract)

115174 Gogolak, G.; Stumpf, Ch. Lehrkanzel fur Neuropharmacologie der Universitat Wien, A-1090 Wien, Wahringerstrasse 13a, Austria Action of anesthetics on the firing pattern of nucleus ruber neurons. *Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin).* 272(4):387-394, 1972.

The action of three typical anesthetic agents, pentobarbital, halothane and trichlorethylene on the activity of single neurons of the pars magnocellularis of the red nucleus wa s investigated in the rabbit and compared with the electrical activity of the cerebellum induced by these drugs. Pentobarbital induces a regular slow wave activity with a frequency between 5 to 25 Hz and a burst firing pattern of single red nucleus neurons, which is correlated with the slow wave rhythm. Halothane induces an irregular low voltage slow wave activity and also an irregular firing pattern of single red nucleus neurons. Trichlorethylene induces a rhythm with a frequency between 40 and 90 Hz and, similar to the case of pentobarbital, a firing pattern of single red nucleus neurons which is correlated with this rhythm. Thus, the differential action of these three agents on the slow wave activity of red nucleus and the cerebellum is reflected in an analogous action on the activity of single red nucleus neurons. 18 references. (Author abstract)

115182 Reyes, Edward; Appelt, Glenn D. School of Pharmacy, Univ.of Colorado, Boulder, CO 80302 Pharmacological aspects of concurrent administration of furosemide and skeletal muscle relaxants. *Journal of Pharmaceutical Sciences.* 61(4):562-566, 1972.

The pharmacological aspects of concurrent administration of furosemide and the skeletal muscle relaxants, d-tubocurarine, succinylcholine, and chlordiazepoxide, were investigated with respect to the effects on diuresis and skeletal muscle relaxation in female albino rats. Administration of d-tubocurarine and chlordiazepoxide concurrently with furosemide produced no significant effects on furosemide induced diuresis. Succinylcholine, when administered concurrently with furosemide, caused a decrease in the volume of urine excreted; other parameters of renal function were not affected. The skeletal muscle relaxant properties of d-tubocurarine, succinylcholine, and chlordiazepoxide were investigated upon concurrent administration of the muscle relaxants with furosemide by an in vivo study and an in situ study. The skeletal muscle relaxant action of succinylcholine was significantly potentiated by pretreatment of the animals with furosemide, both in the exercise wheel study and in the diaphragm - phrenic nerve preparation. A tendency toward an antagonism between d-tubocurarine and furosemide was observed on skeletal muscle relaxation both in vivo and in situ. The effect of d-tubocurarine on blood pressure was also antagonized by treatment of the animal with furosemide. Preliminary spectrophotometric evidence suggests that a complex between furosemide and d-tubocurarine exists, which may possibly explain an antagonism between the two drugs. 16 references. (Author abstract)

115284 Yeh, S.Y.; Mitchell, C.L. Department of Psychiatry, College of Medicine, University of Ken-

tucky, Lexington, KY 40506 Pargyline: a glucuronyl transferase inducer. *Experientia (Basel).* 28(3):298, 1972.

An investigation designed to test the hypothesis that the decrease in the analgesia of morphine in rats treated with pargyline is due to the increasing metabolism of morphine through an induction of glucuronyl transferase is reported. The glucuronide formation of morphine was significantly increased by liver microsomes obtained from pargyline treated rats. Pargyline is a glucuronyl transferase inducer. The mechanism of this action is probably due to an increased metabolism via glucuronide formation. This finding may explain the reason that adverse reactions are seldom observed after administration of morphine to patients treated with monoamine oxidase inhibitors. 10 references.

115289 Forn, J.; Tagliamonte, A.; Tagliamonte, P.; Gessa, G.L. Department of Pharmacology and Therapy, School of Medicine, Barcelona, Spain Stimulation by dibutyryl cyclic AMP of serotonin synthesis and tryptophan transport in brain slices. *Nature New Biology (London).* **237(77):245-247, 1972.**

The effect of 3',5'-adenosine monophosphate (cyclic AMP) and its derivative dibutyryl cyclic AMP on serotonin synthesis and tryptophan transport in rat brain slices was studied. The results show that dibutyryl cyclic AMP stimulates serotonin synthesis in brain slices. Thus, the stimulation of serotonin turnover observed in vivo was a direct effect of the nucleotide and not of the behavioral changes produced. The increase in serotonin synthesis is probably mediated by the increase of brain tryptophan. The failure of cyclic AMP to influence tryptophan and tyrosine transport in brain slices might be attributed to the fact that it penetrates cells with greater difficulty than its less polar derivative and it is easily destroyed by phosphodiesterase. The alterations of serotonin metabolism were obtained using relatively high concentrations of nucleotide so their effects may be pharmacological or they may reflect the action of the endogenous cyclic AMP. The effects are not caused by 5' AMP, indicating that cyclic AMP and not its metabolite is involved. 22 references.

115293 Vernadakis, Antonia. Department of Pharmacology, University of Colorado Medical Center, Denver, CO 80220 Spontaneous seizures in rats treated with chlorpromazine during postnatal development. *Experientia (Basel).* **28(2):173-174, 1972.**

Young (postnatal) rats were treated with chlorpromazine in this investigation to determine dosage levels necessary to produce spontaneous seizures in rats. Type of seizure activity varied with the age of the rats. All doses of chlorpromazine used produced spontaneous seizure like phenomena in 6, 13, and 20-day-old rats, with only the high doses of chlorpromazine producing seizure like activity in 29-day-old rats. This is attributed to a blood brain barrier to the drug which develops after the animal is 20-days-old. It is speculated that the seizure type movements induced by chlorpromazine may be a result of depression of some subcortical and spinal cord inhibitory systems which are ordinarily functioning as early as two days of age in rats. 10 references.

115511 no author. no address Control of serotonin synthesis in rat brain. *Nature (London).* **237(5353):255, 1972.**

The synthesis of 5-hydroxytryptamine (5-HT) from labelled tryptophan was studied in rat brain slices. A reduced rate of conversion was obtained from animals treated a few hours previously with pargyline or pheniprazine (monoamine oxidase inhibitors) when the tissue was incubated in saline medium containing the labelled amino acid. Under such conditions, when the concentration of 5-HT in the tissue had increased to approximately 2.5times the normal level, 5-HT formation was reduced by about 40%. This reduction in 5-HT formation is related to an increase in endogenous indoleamine concentration. It would appear that 5-HT may regulate its own biosynthesis by some form of end product inhibition. The inhibitory effect does seem to involve the rate of transport of the precursor amino acid typtophan into the serotoninergic neurones.

115557 Davies, J.; Watkins, J.C. Department of Pharmacology, School of Pharmacy, Brunswick Square, London W1 Is 1-hydroxy-3-aminopyrrolidone-2 (HA-966) a selective excitatory amino-acid antagonist? *Nature New Biology (London).* **238(80):61-63, 1972.**

The selective action of electrophoretically applied 1-hydroxy-3-aminopyrrolidone-2 (HA-966) in antagonizing L-glutamate and L-aspartate evoked excitation of single neurons in the cerebral cortex of cats is presented. HA-966 was half as potent a depressant as GABA on these responses. In the

case of spontaneously active cells and cells excited by acetylcholine, HA-966 had either no effect or only a weak depressant effect. The weak antiacetylcholene effect of HA-966 was manifested as a faster rate of decay of the prolonged acetylcholine response rather than a reduction of maximum firing rate. It is suggested that HA-966 selectively blocks excitatory amino acid receptors. 11 references.

115558 Tebecis, A.K. Department of Physiology, Australian National University, Canberra, Australia Antagonism of 5-hydroxytryptamine by methiothepin shown in microelectrophoretic studies of neurones in the lateral geniculate nucleus. ***Nature New Biology (London).*** **238(80):63-64, 1972.**

Electrophoretically and intravenously administered methiothepin is shown to have reversibly reduced or blocked the depressant actions of 5-hydroxytryptamine (5-HT) in the lateral geniculate nucleus neurones in cats. Microelectrophoretic methods which circumvent the problem of the blood brain barrier were used. In contrast, methiothepin had no effect on the depressant actions of gamma-aminobutyric acid or dopamine. Further studies on the effect of methiothepin on both the depressant and excitant actions of 5-HT and other monoamines in different areas of the central nervous system are required to establish the value of methiothepin for investigating pathways which release 5-HT as a transmitter. 11 references.

115711 Benzi, G.; De Bernardi, M.; Manzo, L.; Ferrara, A.; Panceri, P.; Arrigoni, E.; Berte, F. Dept.of Pharmacy, Univ.of Pavia, Pavia, Italy Effect of lysergide and nimergoline on glucose metabolism investigated on the dog brain isolated in situ. ***Journal of Pharmaceutical Sciences.*** **61(3):348-352, 1972.**

The glucose uptake and lactic and pyruvic acid formation were investigated in the dog brain isolated in situ during: (1) control conditions, (2) hypoxia by suppression of blood oxygenation, and (3) recovery of oxygenation and intracarotid treatment with saline solution or lysergide or nimergoline at the rate of 0.5ml/min. for 30 min. The hypoxia induced at first an increase and subsequently a decrease in brain glucose uptake, with an increase in both lactic and pyruvic acid formation. The subsequent recovery of blood oxygenation, with intracarotid perfusion with saline solution, induced only a partial recovery of glucose metabolism supported by the increase of the depressed glucose uptake and the decrease of the enhanced lactic and pyruvic acid formation. No significant difference could be demonstrated versus the intracarotid perfusion with lysergide. The intracarotid perfusion with nimergoline induced both an increase in cerebral glucose uptake and a decrease in pyruvate formation, with statistical difference with respect to the change induced by saline solution perfusion; the lactic acid formation remained in the same order of magnitude induced by saline solution perfusion. 26 references. (Author abstract modified)

115712 Stupak, Elliot I.; Bates, Theodore R. Division of Pharmaceutics, School of Pharmacy, Univ.of Connecticut, Storrs, CT 06268 Enhanced absorption and dissolution of reserpine from reserpine-polyvinylpyrrolidone coprecipitates. ***Journal of Pharmaceutical Sciences.*** **61(3):400-404, 1972.**

The in vivo absorption patterns of pure reserpine, a 1:5 w/w reserpine-polyvinylpyrrolidone physical mixture, and a 1:5w/w reserpine-polyvinylpyrrolidone coprecipitate were compared by following the cumulative amounts of reserpine equivalents excreted in the urine as a function of time. The results of these urinary excretion studies demonstrated that both the rate and extent of absorption of reserpine in the rat were significantly enhanced following the oral administration of the coprecipitate; the fraction of the oral dose absorbed was three times greater with the 1:5 reserpine-polyvinylpyrrolidone coprecipitate than with either the pure drug or the 1:5 reserpine-polyvinylpyrrolidone physical mixture. The in vitro dissolution characteristics of the three test preparations at 37 deg correlated very well with the in vitro absorption data. 19 references. (Author abstract)

115714 Haataja, M.; Nieminen, L.; Mottonen, M. Medical Research Laboratories, Laake Oy and Medipolar Oy, Turku, Finland Effect of levodopa upon plasma levels of 17-hydroxycorticosterone. ***Journal of Pharmaceutical Sciences.*** **61(3):481-482, 1972.**

The effect of chronic levodopa (L-Dopa) treatment upon plasma levels of 17-hydroxycorticosterone (17-HC) was studied in dogs. Three groups were used: one was a control; second received 150mg/kg/day of L-Dopa; the third group received 300mg/kg/day for three months. 17-HC was determined daily from blood samples. No sig-

nificant differences were observed in the values. No remarkable differences occurred between sexes in the control group or the therapy groups. No significant fluctuations of the plasma levels of 17-HC were observed during the treatment. 9 references.

115715 Cohen, I.; Vogel, W.H. Dept.of Pharmacology, Jefferson Medical College, Thomas Jefferson Univ., Philadelphia, PA 19107 Determination and physiological disposition of dimethyltryptamine and diethyltryptamine in rat brain, liver and plasma. *Biochemical Pharmacology (Oxford).* 21(8):1214-1216, 1972.

The concentrations and physiological disposition of dimethyltryptamine (DMT) and diethyltryptamine (DET) in rat brain, liver and plasma were determined as a function of time and dose. Data indicates that DMT and DET have almost equal potency and the presence of both compounds in the rat central nervous system suggests a central site of action and implicates both compounds and not a metabolite as the active principle. A comparison of the minimal doses of DMT and DET necessary to produce abnormal behavior with various other tryptamine analogs was made. The chemistry of both DMT and DET in the central nervous system is discussed. 23 references.

115716 Mrsulja, B.B.; Rakic, L.M. Institute of Biochemistry, Faculty of Medicine, 11000 Belgrade 7, Yugoslavia Influence of oxotremorine on glycogen content in various brain structures of rat brain. *Biochemical Pharmacology (Oxford).* 21(8):1209-1210, 1972.

The influence of oxotremorine (2'-oxo-1:4-dipyrrolidinobutyne) on glycogen content in various brain structures of rat brain was investigated. The brain structures examined were the cortex cerebri, caudate, thalamus, cortex cerebelli, and caudal brain stem. The influence of atropine and propanolol on the glycogenolytic effect of oxotremorine was also examined. Atropine as well as propanolol prevents the glycogenolytic effect of oxotremorine in rat brain. Results are similar to those obtained with physostigmine. Results are discussed in light of other studies. 12 references.

115720 Elwood, J.Clint; Richert, Dan A.; Westerfield, W.W. Dept.of Biochemistry, State Univ.of New York, Upstate Medical Center, Syracuse, NY 13210 A comparison of hypolipidemic drugs in the prevention of an orotic acid fatty liver. *Biochemical Pharmacology (Oxford).* 21(8):1127-1134, 1972.

The prevention of a fatty liver by adding test substances to a 1% orotic acid diet was used to obtain assay curves for various hypolipidemic drugs. The following drugs had approximately the same activity in this test: ethyl p-chlorophenoxyisobutyric acid (CPIB); p-phenoxyphenyl methanesulfonate and N,N-dimethyl-N'-(4-phenoxyphenyl) sulfamide; and 2,2'-((1-methyl-4,4'-diphenylbutylidine)-bis-(phenyleneoxy)) bis-triethylamine-citrate. 1-Methyl-4-piperidyl-bis-(p-chloro-phenoxy) acetate (SaH 42348) was two to three times as active, and 2-methyl-2-(p-1,2,3,4-tetrahydro-1-napthylphenoxy) propionic acid (Su 13437) was 10 times as active as CPIB. On the same weight basis, choloxon (D-thyroxine; D-T4) was 80-90 times as active. Dilantin, L-thyropine (L-T4), nicotinic acid, and cholestyramine had little or no effect. Adenine, allopurinol 04-hydroxytyrazolo (3,4-d) pyrimidine0 and 5,5'-diphenyl-2-thiohydantoin (DPTH) were as active as most of the drugs in preventing triglyceride deposition. The only substances which increased liver alpha-glycerophosphate dehydrogenase were: CPIB, Su 13437, SaH 42348, D-T4 and L-T4. The lipotropic effect of these drugs was not mediated through this enzyme. Feeding orotic acid alone practically eliminated the pre-beta and beta-lipoprotein (betaLP) band from the serum gel electrophoresis, but the intensity of the beta band was restored by the active drugs in proportion to their dosages; inactive substances did not restore the betaLP band. A quick screening procedure was developed for substances which intensify the serum betaLP band. 12 references. (Author abstract modified)

115721 Westerfeld, W.W.; Elwood, J.Clint; Richert, Dan A. Dept.of Biochemistry, State Univ.of New York, Upstate Medical Center, Syracuse, NY 13210 Effect of clofibrate on the handling of dietary and liver fat. *Biochemical Pharmacology (Oxford).* 21(8):1117-1125, 1972.

The role of liver alpha-glycerophosphate dehydrogenase (GPD) and malic enzyme on the para-chlorophenoxybutyrate (CPIB) effect on fat metabolism in rats was evaluated. CPIB had a marked effect on the handling of erogenous fat by rats. After an oral fat load, the serum triglyceride response was plotted, and the areas under such curves were compared with the amounts of GPD and malic enzyme present in the liver. CPIB and L-thyroxine (T4) increased these enzyme activi-

ties; diphenylthiohydantoin and imidazole were also used to inhibit the induction of GPD and enhance the malic enzyme response respectively. Changes in these enzyme activities did not appear to be involved in the CPIB effect on the disposition of oral fat. CPIB completely prevented or corrected the fatty liver produced by feeding orotic acid to intact or thyroidectomized rats, and gave a strong beta-lipoprotein band in serum gel electrophoresis; T4 had only a small effect. The effect of CPIB on fat metabolism was therefore not mediated through its enhancement of T4 effects in the liver. 37 references. (Author abstract modified)

115963 Koss, M.C.; Wang, S.C. Dept.of Pharmacology, College of Physicians and Surgeons of Columbia Univ., New York, NY 10032 Effects of reserpine in centrally and peripherally evoked nictitating membrane responses in the cat. ***American Journal of Physiology.*** **222(4):906-913, 1972.**

Previously determined brainstem loci for activation of the nictitating membrane (NM) were utilized in studying the acute effects of reserpine in intact anesthetized and decerebrate cats. In some experiments two brainstem loci (lateral and midline) were used in constrasting the central effects of reserpine. In others, NM responses were evoked from the preganglionic cervical sympathetic nerve and central (lateral or midline) sites. In all preparations, reserpine was found to decrease the magnitude of the NM responses. In the intact preparations, NM contractions evoked from central loci and the peripheral nerve declined at the same rate to approximately 60% of control after 150 min. The same was true for central (lateral) and peripheral evoked responses in midcollicular decerebrate preparations. On the other hand, NM contractions elicited from the central (midline) loci after midcollicular decerebration were further depressed to less than 10% of control after 150 min. This selective central (midline) action of reserpine in the decerebrate animal was also demonstrated by recording centrally evoked activity along the cervical sympathetic nerve. In all cases, reserpine depressed the nictitating membrane response by means of its peripheral action. 24 references. (Author abstract modified)

116087 Burstein, Sumner; Rosenfeld, Jack; Wittstruck, Thomas. Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545 Isolation and characterization of two major urinary metabolites of delta(1)-tetrahydrocannabinol. ***Science.*** **175(4033):422-423, 1972.**

Two of the major metabolites that appear in rabbit urine after the administration of delta(1)-tetrahydrocannabinol have been isolated and their structures have been tentatively established. The available evidence indicates that they are 7-carboxy-delta(1)-tetrahydrocannabinols with an additional hydroxyl group on the side chain. The substances occur both free and as conjugates. 16 references. (Author abstract)

116577 Eble, J.N.; Gowdey, C.W.; Vane, J.R. Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons, Lincoln's Inn Fields, London WC2, England Blood concentrations of adrenaline in dogs after intravenous administration of 5-hydroxytryptamine. ***Nature New Biology (London).*** **238(86):254-256, 1972.**

Release of catecholamines from the adrenal medulla of dogs following intravenous injections of 5-hydroxytryptamine (5-HT) was reported. The catecholamine is identified as adrenaline; and the enhancement of the release by treatment of the dog with hexamethonium is demonstrated. The results show that adrenaline is released into the circulation following intravenous 5-HT in sufficient quantities to affect resistance in the perfused hind leg of the dog and to contribute to the systemic blood pressure effects of intravenously administered 5-HT. 13 references.

116674 Bolger, L.; Brittain, R.T.; Jack, D.; Jackson, M.R.; Martin, L.E.; Mills, J.; Poynter, D.; Tyers, M.B. Research Division, Allen and Hanburys, Ware, Hertfordshire, England Short-lasting, competitive neuromuscular blocking activity in a series of azobis-arylimidazo-(1,2-a)-pyridinium dihalides. ***Nature (London).*** **238(5363):354-355, 1972.**

The short-lasting competitive neuromuscular blocking activity of the azobis-arylimidazo-(1,2-a)-pyridinium derivatives on chicks, cats, dogs, and monkeys is described. The drugs have a rapid onset of action which do not affect the cardiovascular system at therapeutic doses and can be rapidly reversed by neostigmine. The compounds were prepared as dibromides or dichlorides. All the active compounds caused flaccid paralysis which lasted for only one to two minutes without sign of muscle fasciculations. The most potent compound AH 8165 was about

as active as succinylcholine. It was concluded that large doses of AH 8165 caused partial blockade of autonomic ganglia and thus lowered blood pressure. 5 references.

116675 Okada, F.; Saito, Y.; Fujieda, T.; Yamashita, I. Department of Psychiatry and Neurology, Hokkaido University School of Medicine, Sapporo, Japan Monoamine changes in the brain of rats injected with L-5-hydroxytryptophan. ***Nature (London).*** **238(5363):355-356, 1972.**

L-5-hydroxytryptophan (L-5HTP) induced regional changes in central monoamine concentrations in rat brain and plasma corticosterone levels in relation to these changes were investigated. A large dose of L-5HTP is capable of increasing plasma corticosterone level. This finding may be related to the regional monoamine changes in the brain, especially to the increased serotonin level in the hippocampus. Animals injected with the larger dose showed a decreased voluntary movement combined with general muscle tremors. Therefore, this rise of plasma corticosterone level may be regarded as a result of nonspecific stress induced by this amine. 19 references.

116680 Collier, H.O.J.; Francis, D.L.; Schneider, C. Miles Laboratories Limited, Stoke Poges, Slough, Buckinghamshire, England Modification of morphine withdrawal by drug interacting with humoral mechanisms: some contradictions and their interpretation. ***Nature (London).*** **237(5352):220-223, 1972.**

Modification of morphine withdrawal by drugs interacting with humoral mechanisms in rats is discussed. Some contradictions are given and interpreted. Atropine, para-chlorophenylalanine and indomethacin modify some effects of morphine withdrawal in the rat. Factors determining the intensity and even the direction of this modification include the particular withdrawal effect observed and the time in the course of dependence when the modifying drug is given. These findings suggest that morphine dependence is multipartite and that acetylcholine, 5-hydroxytryptamine, and prostaglandin play intimate parts in various elements of dependence. 16 references. (Author abstract modified)

116778 Doggett, N.S.; Spencer, P.S.J. Pharmacology Laboratories, Welsh School of Pharmacy, University of Wales, Wales Ouabain and the onset of the blood-brain barrier in neonate chicks. ***Nature (London).*** **237(5357):513-514, 1972.**

Ouabain was used to study the onset of the blood brain barrier in neonate chicks. To obtain evidence that the depressant effects result from a direct action on the central nervous sytem, young chicks in which adult blood brain characteristics were not reported to be present until about the fourth week of life were used. These experiments provide further evidence for a potent central, depressant effect of ouabain. Of particular interest is the rapidity with which insensitivity to these effects develops with the age of the chick. It seems likely that the blood brain barrier develops at different rates for different compounds depending partially on the molecular structures of those compounds. Changes in the integrity of the blood brain barrier may also reflect the development of fully functional neurotransmitter systems within the brain. It is thus impossible to define the degree of maturity of the blood brain barrier in the chick unless it is related to specific pharmacological agents. 8 references.

116851 Sullivan, John L.; Segal, David S.; Kuczenski, Ronald T.; Mandell, Arnold J. Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, CA 92037 Propranolol-induced rapid activation of rat striatal tyrosine hydroxylase concomitant with behavioral depression. ***Biological Psychiatry.*** **4(3):193-203, 1972.**

The effect of propranolol, a beta-adrenergic blocking agent, on tyrosine hydroxylase activity in the rat brain and the concomitant effects on behavioral activity was determined. Acute propranolol administration in rats produced a dose dependent, short latency, reversible increase in the total specific activity of striatal tyrosine hydroxylase, the rate limiting enzyme in catecholamine biosynthesis. The experimental animals manifested a temporally related behavioral depression. A similar combination of biochemical and behavioral events followed the acute administration of reserpine. Activation of tyrosine hydroxylase under these circumstances may present a rapid compensatory response to the functional impairment of central catecholamine synapses. From related work in progress, it is speculated that this effect is due to a drug promoted, membrane activation binding of the biosynthetic enzyme at nerve endings. The similarity of propranolol's action to that of reserpine in this neurochemical system suggests the possibility that the clinical use of propranolol may represent a potential source of depression when

used in patents with cardiovascular disease. 40 references. (Author abstract modified)

116954 DeGroat, W.C. Department of Pharmacology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213 GABA-depolarization of a sensory ganglion: antagonism by picrotoxin and bicuculline. ***Brain Research (Amsterdam).*** **38(2):429-432, 1972.**

Evidence for a depolarizing action of gamma-aminobutyric acid (GABA) on cat neurons in the vagal sensory ganglion (nodose ganglion) is reported. The action was specific for GABA, i.e.,other closely related amino acids were inactive, and was selectively blocked by known GABA antagonists. It is suggested that GABA would have a similar action on the central terminals of these neurons. The depolarizing responses to GABA were reduced or completely abolished by the intraarterial administration of either picrotoxin or bicuculline but were unaffected by strychnine. The actions of the antagonists were transient. This suggests a competitive type of blocking action. It is suggested that a high chloride concentration is a general property of peripheral nerve cells and that this property allows the nervous system to use the same transmitter in one case to hyperpolarize central nerve cells and in the other to depolarize the terminals of peripheral sensory nerve cells. 12 references.

116957 Placidi, Gian Franco; Masuoka, David T.; Earle, Robert W. Psychiatry Clinic, University of Pisa, Pisa, Italy Distribution of (14C)amphetamine in mouse brain: an autoradiographic study. ***Brain Research (Amsterdam).*** **38(2):399-405, 1972.**

The localization and distribution of C14-amphetamine in mouse brain was studied by an autoradiographic technique and by thin layer chromatography. Thin layer chromatography revealed that radioactivity in the brain is chiefly due to unchanged amphetamine. The highest content was found in the cerebral cortex, hippocampus, thalamus, septum and basal ganglia. The possible relationship of this localization to the site of action of amphetamine and the distribution of catecholamine nerve terminals is discussed. 16 references. (Author abstract)

117389 Booth, David A. Laboratory of Experimental Psychology, University of Sussex, Brighton, England BN1 9QY Some characteristics of feeding during streptozotocin-induced diabetes in the rat. ***Journal of Comparative & Physiological Psychology.*** **80(2):238-249, 1972.**

The characteristics of feeding during streptozotocin induced diabetes were studied in the rat. At four to nine days after streptozotocin injection (50mg/kg) rats show abbreviated intermeal intervals. There is also a lack of proportionality of intermeal interval duration to size of the preceding meal, which probably accounts for the hyperphagia which develops at four to six days and increases over two weeks. Such effects are not seen in the first three days, even though the rats are glucosuric and polydipsic within 24 hrs of streptozotocin treatment. In contrast, decreases in basal feeding rate and in meal size do begin to develop in the first three days of diabetes. It is suggested that aversion to the diet develops immediately on insulin deficiency, but that the satiety deficits and hyperphagia in chronic diabetes are secondary to considerable changes in body composition. 41 references. (Author abstract)

117610 Cowan, A.; Whittle, B.A. Pharmaceutical Research Laboratories, Reckitt and Coleman, Pharmaceutical Division, Hull, England Inability of antidepressants and morphine to reverse reserpine-induced hypothermia in adrenalectomized mice. ***British Journal of Pharmacology (London).*** **44(2):353P-354P, 1972.**

The effect of adrenalectomy on the thermogenic response of antidepressants and morphine in reserpinized mice was investigated. Adrenalectomized mice showed an enhanced sensitivity to the temperature-lowering effect of reserpine. It was not possible to demonstrate reversal of reserpine induced hypothermia in adrenalectomized mice with the following compounds which effect a reversal in normal mice: D-amphetamine, desmethylimipramine, morphine, diprenorphine, and the dihydrocodeinone R & S 336-M. Since the thermogenic effect of these compounds was only demonstrated in reserpinized mice with functional adrenal glands, this response would appear to be a peripheral phenomenon mediated by the release of catecholamines from the adrenal medulla. 3 references.

117616 Guldberg, H.C.; Marsden, C.A. Dept.of Pharmacology, Univ.of Bergen, Bergen, Norway Brain monoamines and the increase in motor activity in the rat after amphetamine. ***British Journal of Pharmacology (London).*** **44(2):347P-348P, 1972.**

A study to determine whether 5-hydroxytryptamine and/or noradrenaline have a function in amphetamine induced rotational motor activity in the rat is presented. The results suggested that 5-hydroxytryptamine was not involved in the amphetamine induced rotation seen in rats with unilateral lesions in the substantia nigra but that a similar rotational motor activity could be produced by the destruction of a system other than the nigrostriatal dopamine system. It is suggested that the stereotyped behavior produced by amphetamine may be due to dopamine release and the locomotor stimulation to the release of noradrenaline. 3 references.

117617 Paton, W.D.M.; Temple, Diana M. Dept.of Pharmacology, Univ.of Oxford, Oxford OX1 3QT, England Effects of chronic and acute cannabis treatment upon thiopentone anaesthesia in rabbits. ***British Journal of Pharmacology (London).*** **44(2):346P-347P, 1972.**

The effects of chronic and acute cannabis treatment upon thiopentone anesthesia was studied in rabbits. Four groups were used: acute cannabis stabilized with Tween 80; chronic cannabis stabilized with Tween 80; Tween 80 alone; and untreated. The acute cannabis and chronic cannabis groups required a mean dose of thiopentone to reach the anaesthetic endpoint which was 26-27% smaller than for their respective untreated or chronic Tween controls. The latter did not differ significantly in the dose required. The rate of recovery was indistinguishable in all four groups of animals. One acute cannabis treated animal, however, which was given the same dose of thiopentone as the control group, being therefore more deeply anaesthetized, took three times longer to recover. It is concluded that cannabis potentiates thiopentone anaesthesia in the rabbit, and that the pontentiation lasts at least five days longer than a period of chronic cannabis administration. 1 reference.

117618 Bramwell, G.J. Dept.of Pharmacology, School of Pharmacy, Univ.of London, 29/39 Brunswick Sq, London WC1N 1AX, England Effect of imipramine on unit activity in the midbrain raphe of rats. ***British Journal of Pharmacology (London).*** **44(2):345P-346P, 1972.**

The effect of imipramine (I) on unit activity was examined in the midbrain raphe of rats. Unit activity of the raphe nuclei were recorded in male rats under light anesthesia. All units tested, responded to I with a slowing or cessation of firing, although the sensitivity of the units varied widely. Recovery from I did not occur within 30 min of onset thus the effect is persistent. The inhibitory effect is likely to be related to an increase of 5-hydroxytryptamine. 4 references.

117619 Clarke, G.; Davies, J.; Straughan, D.W. Dept.of Pharmacology, School of Pharmacy, Univ.of London, 29/39 Brunswick Sq, London WC1N 1AX, England Iontophoretic study of the central anticholinergic properties of BRL 1288. ***British Journal of Pharmacology (London).*** **44(2):344P-345P, 1972.**

An iontophoretic study of the central anticholinergic properties of 2-(ethyl-n-propylamino)ethyl-alpha-alpha-diphenylglycollate hydrochloride (BRL-1288) was made with cats and with isolated frog siatic nerve. The action of BRL-1288 was compared with those of atropine and procaine on acetylcholine and L-glutamate excited neurons. BRL-1288 reduced the excitant action of acetylcholine. However, this action of BRL was not specific for acetylcholine since the excitatory effect of L-glutamate was also reduced. Moreover, BRL-1288 was more effective against glutamate. Atropine was at least twice as effective as BRL-1288, on a current basis, in reducing the excitant action of acetylcholine and, unlike BRL, it produced a long lasting effect. However, atropine had only half the activity of BRL-1288 against neurons excited by L-glutamate and recovery was rapid. When tested with isolated frog siatic nerve, BRL-1288, on a molar basis, was two to three times as potent as procaine and 100 times as potent as atropine. Its central anticholinergic properties are particularly weak on cortical neurons. 3 references.

117622 Ceasar, P.M.; Sharman, D.F. Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge, England Studies on the glycol metabolites of noradrenaline in mouse brain. ***British Journal of Pharmacology (London).*** **44(2):340P-341P, 1972.**

The glycol metabolites of noradrenaline in the mouse brain are presented. Noradrenaline can be metabolized to 1-(4-hydroxy-3-methoxyphenyl)-1,2-ethanediol (MOPEG) and 1-(3,4-dihydroxyphenyl)-1,2-ethanediol (DOPEG) in animal tissues. When groups of mice were exposed to a low temperature (-5 to -15 degree C) the concentration of MOPEG in the hypothalamus was increased

and the concentration of DOPEG almost doubled. After treatment with drugs which inhibit monoamine oxidase it was found that DOPEG disappeared at a rate four times that of MOPEG. Tropolone administration doubled the concentration of DOPEG. Reserpine, desmethylimipramine, and cocaine produced no change in either of the glycols. 1 reference.

117623 Harris, M.; Hopkin, Judy; Neal, M.J. Dept.of Pharmacology, School of Pharmacy, Univ.of London, Brunswick Sq., London, WC1N 1AX, England Effect of centrally acting drugs on the uptake of gamma-aminobutyric acid by the brain. Effect of centrally acting drugs on the uptake of gamma-aminobutyric acid by the brain. *British Journal of Pharmacology (London).* 44(2):339P-340P, 1972.

The effect of centrally acting drugs on the uptake of gamma-aminobutyric acid (GABA) by the rat brain was examined. Sixty-five compounds were tested for possible inhibitory effects on the uptake of 3H-GABA. More than half of the drugs tested produced a significant reduction in the uptake of 3H-GABA by the contex, but the only groups of centrally acting drugs in which all members consistently produced inhibition of uptake were the phenothiazines and the tricyclic antidepressants. Other compounds which had a relatively powerful inhibitory effect on uptake of 3H-GABA were: p-chloromercuriphenylsulphonate, L-2,4-diaminobutyric acid, haloperidol, apomorphine and diphenhydramine. These results suggest that it is unlikely that centrally acting drugs act by specifically affecting the uptake process for GABA in the brain, since the concentrations of drug required to reduce the uptake of GABA also have marked effects on the uptake of other amino acids and on biogenic amines. 1 reference.

117624 Gilbert, J.C. Dept.of Pharmacology, Univ.of Aberdeen, Aberdeen, Scotland Effects of phenobarbitone on glucose transport and membrane ATP-ase activities of cerebral cortex. *British Journal of Pharmacology (London).* 44(2):338P-339P, 1972.

The effects of phenobarbitone on glucose transport and membrane ATPase activities of the cerebral cortex were examined in the guinea pig. Glucose metabolism was negligible. At 37 degrees C, glucose uptake by the slices was rapid and its volume of distribution soon exceeded that of raffinose. The kinetics of permeation of glucose into the nonraffinose compartment conformed to carrier transport kinetics and phenobarbitone did not influence the process. At 37 degrees C, glucose efflux from slices was rapid and was not significantly influenced by phenobarbitone. It is suggested that iodoacetamide can prevent stimulation of sugar transport by some drugs. Glucose uptake at 1 degree C, in the absence of iodoacetamide, was slow and was significantly stimulated by phenobarbitone; the volume of distribution of glucose did not exceed that of raffinose and the kinetics of uptake were compatible with a simple diffusion process. Phenobarbitone sodium did not significantly alter the activity of ATPase. It was concluded that the effect of phenobarbitone on sugar transport is probably mediated by influencing directly the apparent affinity of carrier for sugar rather than indirectly by influencing active sodium efflux from the cell. 4 references.

117625 Adcock, Jennifer J.; Gilbert, J.C. Dept.of Pharmacology, Univ.of Aberdeen, Aberdeen, Scotland Effects of phenobarbitone and leptazol on rat brain lysomes. *British Journal of Pharmacology (London).* 44(2):337P-338P, 1972.

The effects of phenobarbitone on release of acid phosphatase from lysosomes of the rat cerebral cortex have been determined: 1) after injecting phenobarbitone into rats and subsequently incubating the mitochondrial fraction in 0.25 M sucrose solution and 2) after incubating the mitochondrial fraction from untreated animals in media containing phenobarbitone. Results suggest that phenobarbitone stabilizes brain lysosomes to a significant extent. 6 references.

117626 Bowers, M.B., Jr.; Roth, R.H. Dept.of Psychiatry, Yale Univ.School of Medicine, New Haven, CT Interaction of atropine-like drugs with dopamine-containing neurones in rat brain. *British Journal of Pharmacology (London).* 44(2):301-306, 1972.

A variety of atropine like drugs effective in the treatment of drug induced extrapyramidal syndromes (benztropine mesylate, procyclidine hydrochloride, benzhexol hydrochloride, ethopropazine hydrochloride, atropine sulphate, and atropine methonitrate) have been investiaged with regard to their interaction with dopamine containing neurons in rat brain. Under some conditions benztropine, trihexyphenidyl, atropine and ethopropazine significantly antagonized the chlorpromazine induced increase in subcortical concen-

trations of homovanillic acid. Most of the atropine like drugs investigated also decreased the turnover of dopamine in the subcortex as measured by following the disappearance of dopamine after administration of alpha-methyl-p-tyrosine. These findings are suggestive that an imbalance between a dopaminergic and cholinergic system might be closely linked to the pathogenesis of extrapyramidal movement disorders. 19 references. (Author abstract)

117627 Binini, R.; Bonaccorsi, A.; Garattini, S.; Morselli, P.L.; Muscettola, G. Instituto di Richerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy Uptake of desipramine by the rat vas deferens. ***British Journal Of Pharmacology (London).*** **44(2):262-270, 1972.**

Determinations of desipramine in the isolated rat vas deferens were carried out in order to study the uptake of the drug and to evaluate how this may correlate with the effect on noradrenaline (NA) induced contraction. Vasa deferentia, in contact with desipramine for 10 min accumulated the drug about sixfold in respect to the medium. When the time of contact was prolonged to four hours, desipramine was concentrated about 100 times. The uptake was not saturable and it was not affected by the presence of imipramine, cocaine, ouabain, dinitrophenol and iodoacetate. No metabolic process is involved although the accumulation of desipramine is temperature dependent. The release of desipramine from the vas deferens is exponential and it is not affected by the presence of plasma in the medium. No clear correlation was found between tissue concentration of the drug and the potentiation of noradrenaline responses, probably because of the high nonspecific binding of the drug to tissue components which may mask specific binding sites for NA resulting in potentiation. However, the concentration of desipramine seems to correlate with the inhibition of NA effect which occurs at high doses of desipramine. 19 references. (Author abstract modified)

117628 Paton, W.D.M.; Pertwee, R. G. Paton, W.D.M.; Pertwee, R. G. Dept.of Pharmacology, Univ.of Oxford, Oxford OX1 3QT, England Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. ***British Journal of Pharmacology (London).*** **44(2):250-261, 1972.**

The effect of cannabis and some of its constituents on pentobarbitone sleeping time and phenazone metabolism was investigated in mice. Cannabis extract prolonged sleeping time in a thermally neutral environment in which hypothermia does not occur. The prolongation was dose related. Under these conditions, ether sleeping time was not prolonged. Cannabis extract inhibited the aerobic metabolism of phenazone by a microsome rich 9,000 g supernatant of mouse liver homogenate capable of nicotinamide adenine dinucleotide phosphate generation. Tetrahydrocannabinol delta1-(delta1-THC) prolonged pentobarbitone sleep and inhibited phenazone metabolism, but its action was limited, and could not account for the effect of the extract. The carotenes and water soluble fractions of the extract were inactive on pentobarbitone sleep. Cannabidiol was strongly active by both tests; in vivo prolonged sleep by 190%, and in vitro inhibited phenazone metabolism 20%. The prolongation of pentobarbitone sleep by cannabis extract in a dose of 200mg/kg, intraperitoneally, was maximal when given 30 min before the pentobarbitone, still present at three hours, but undetectable at 24 hours. No phase of enhanced metabolism at 24 or 48 h after single cannabis injection was detected. It is concluded that cannabis extract inhibits microsomal activity of mouse liver, chiefly by virtue of its cannabidiol content. It is probable that cannabis consumption by man could lead to altered disposal of many other drugs, used in medicine or otherwise. 30 references. (Author abstract modified)

117629 Freudenthal, R.I.; Martin, J.; Wall, M.E. Chemistry and Life Sciences Laboratory, Research Triangle Institute, P.O.Box 12194, Research Triangle Park, NC 27709 Distribution of delta(9)-tetrahydrocannabinol in the mouse. ***British Journal of Pharmacology (London).*** **44(2):244-249, 1972.**

The distribution of delta (9)-tetrahydrocannabinol-14C in the pregnant and nonpregnant mouse is reported. High concentrations of radiolabel can be seen in the maternal liver, spleen, lungs, brown fat, adrenal glands, mammary glands, yolk sac placenta and corpora lutea. In the pregnant mouse delta(9)-THC crosses the placenta and enters the fetuses in very low concentrations, with no apparent selective intrafetal radiolabel accumulation sites. Autoradiograms showing the distribution of 14C-cannabinoid two hours after dosing are presented. A small amount

of maternal liver and fetal tissue was removed from the mice, used for autoradiography and extracted with ethyl acetate. Most of the radiolabel in these tissues was solvent extractable and was separated by thin layer chromatography into two fractions, THC and metabolites. It appears that most of the cannabinoid is present in a free rather than conjugated form. 7 references. (Author abstract)

117630 Clark, D.W.J.; Laverty, R.; Phelan, E.L. Dept.of Medicine, Wellcome Medical Research Institute, Univ.of Otago, P.O.Box 913, Dunedin, New Zealand Long-lasting peripheral and central effects of 6-hydroxydopamine in rats. ***British Journal of Pharmacology (London).*** **44(2):233-243, 1972.**

Peripheral and central effects of 6-hydroxydopamine were examined in rats, newborn rats treated with 6-hydroxydopamine hydrobromide (50-150mg/kg) a widespread and long lasting dose related sympathectomy was demonstrated. When rats given 6-hydroxydopamine (100 mg/kg) in the neonatal period were killed at 10 weeks the concentration of noradrenaline (NA) in the heart, mesentery and vas deferens was significantly reduced. There was no alteration in the catecholamine content of the adrenal glands. The amplitude of the responses of perfused mesenteric arteries from 6-hydroxydopamine treated rats to intraarterial noradrenaline was not increased, compared with controls, but the duration of responses was increased. 6-Hydroxydopamine given to newborn rats caused a long lasting depletion of noradrenaline in three of the five regions of the central nervous system (cortex, cerebellum and spinal cord) studied. The concentration of NA in the pons - medulla was increased, but in the thalamic region was unchanged. The treated rats showed significantly lower exploratory activity. Treatment of newborn rats with 6-hydroxydopamine thus has striking and long-lasting effects on peripheral and central adrenegic systems. 23 references. (Author abstract modified)

117632 Cashin, C.H. Dept.of Pharmacology, Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey, England Effect of sympathomimetic drugs in eliciting hypertensive responses to reserpine in the rat, after pretreatment with monoamineoxidase inhibitors. ***British Journal of Pharmacology (London).*** **44(2):203-209, 1972.**

The effects of some rapidly metabolized sympathomimetic amines, such as beta-phenylethylamine and p-tyramine, in eliciting hypertensive responses to reserpine in the anaesthetized rat, have been studied. Retardation of metabolism, by pretreatment with the monoamineoxidase inhibitors iproniazid or phenelzine, causes beta-phenylethylamine (which in untreated rats has no effect) to induce hypertensive responses to reserpine. Tyramine and other hydroxy substituted phenylethylamines are much less active in this respect, probably because of relatively poor lipid solubility. Hypertensive responses to reserpine are due to catecholamine release, which is believed to be from stores made accessible to indirectly acting sympathomimetic amines with high lipid solubility by an action of reserpine on cell membranes. 10 references. (Author abstract)

118070 Miller, A.L.; Hawkins, R.A.; Harris, R.L.; Veech, R.L. Section on Neurochemistry, NIMH, Saint Elizabeths Hospital, Washington, DC The effects of acute and chronic morphine treatment and of morphine withdrawal on rat brain in vivo. Rockville, Md., NIMH, 1972. 22 p.

The effects of acute and chronic morphine, nalorphine, acetazolamide, and 10% carbon dioxide on brain metabolite concentrations of 24 hour starved rats were studied. A single dose of morphine (20mg/kg body weight) caused an increase in brain glucose concentration and decreased concentrations of lactate, pyruvate, citrate, alpha-oxoglutarate, malate, and creatine phosphate after 30 min. No changes were found in adenosine nucleotide concentrations. The same dose of morphine raised arterial carbon dioxide and decreased pH and dioxide. Nalorphine, an antagonist of morphine, caused essentially no changes in brain metabolite concentrations in normal rats. When nalorphine was administered to rats previously treated with morphine three times daily for two weeks, there was an increase in brain glucose, lactate, pyruvate, and citrate concentrations. Acetazolamide, and inhibitor of carbonic anhydrase, and 10% carbon dioxide raised the arterial carbon dioxide. Both acetazolamide and 10% carbon dioxide caused changes in brain metabolite concentrations similar to acutely administered morphine. No changes in adenosine nucleotide concentrations were found. The results indicate that the effects of morphine on brain metabolite concentrations may be accounted for by the increased carbon dioxide. These findings constitute a consistent pattern of metabolite correlates of acute morphine administration, morphine addic-

tion, and withdrawal from morphine addiction. 37 references. (Author abstract modified)

118359 Farrow, John T.; Van Vunakis, Helen. Graduate Department of Biochemistry, Brandeis University, Waltham, MA 02154 Binding of d-lysergic acid diethylamide to subcellular fractions from rat brain. *Nature (London).* 237(5351):164-166, 1972.

The binding of LSD to subcellular fractions (synaptosomes, myelin, and mitochondria) from rat brain was studied. Binding of LSD took place with synaptosomes but not with myelin or mitochondria. Serotonin, norepinephrine, tryptamine, and ergonovine inhibited this binding, but glutamate showed only slight inhibition. The cross-tolerance of mescaline, psilocybin, and LSD suggests similar central nervous system sites of action. 19 references.

118405 Guidotti, A.; Weiss, B.; Costa, E. Laboratory of Preclinical Pharmacology, NIMH, St.Elizabeths Hospital, Washington, DC 20032 Adenosine 3',5'-monophosphate concentrations and isoproterenol-induced DNA synthesis in mouse parotid gland. (Unpublished paper). Washington, DC NIMH, 1972, 15 p.

The relationship between the concentration of adenosine 3',5'-monophosphate (cyclic 3',5'-AMP) and the rate of synthesis of DNA was studied in the mouse parotid gland. Isoproterenol produced a dose related increase in the concentration of cyclic 3',5'-AMP. This increase was maximum within 10 minutes and persisted longer than two hours. The rise of cyclic 3',5'-AMP in parotid gland was several times greater and longer lasting than that seen in lung and heart, even though the concentration of isoproterenol in the parotid gland was lower than in lung and heart. Pretreatment of mice with aminophylline potentiated the isoproterenol induced increase of cyclic 3',5'-AMP in parotid gland. Isoproterenol also increased the incorporation of 3H-thymidine into DNA and the total amount of DNA per gland as measured 28 hours after the injection. These increases were potentiated by pretreating the animals with aminophylline. In parotid gland a positive relationship was found between the concentration of cyclic 3',5'-AMP and the synthesis rate of DNA irrespective of whether isoproterenol was administered alone or in conjunction with aminophylline. Moreover, the increased concentration of cyclic 3',5'-AMP induced by these drugs preceded any changes in the synthesis of DNA. These results suggest that in parotid gland cyclic 3',5'-AMP may play a role in the acceleration of DNA synthesis elicited by isoproterenol. 72 references. (Author abstract modified)

118486 Costa, E.; Guidotti, A. Laboratory of Preclinical Pharmacology, NIMH, St.Elizabeths Hospital, Washington, DC 20032 The role of 3', 5'-cyclic adenosine monophosphate in the regulation of adrenal medullary function. (Unpublished paper). Washington, DC, NIMH, 1972, 24 p.

The role of 3',5'-cyclic adenosine monophosphate in the transynaptic control of tyrosine hydroxylase in the adrenal medulla of the rat was studied. Carbamylcholine increases cyclic AMP concentrations in medulla and cortex; the cyclic AMP increase elicited by carbamylcholine in cortex is much smaller than that caused by aminophylline injections and ACTH. The increase of cyclic AMP caused by carbamylcholine in medulla compares with the response elicited by aminophylline and massive does of ACTH. The carbamylcholine can increase cyclic AMP concentration after cholinergic nerves have been severed. Carbamycholine increases tyrosine hydroxylase activity in both intact and denervated gland; ACTH, theophylline, and reserpine can increase tyrosine hydroxylase activity only if the splancnic nerve is intact. ACTH increases cyclic AMP in cortex and adrenal medulla; the threshold dose of ACTH to elicit such a response is lower for medulla than for adrenal cortex. ACTH increases also tyrosine hydroxylase activity but this effect occurs after a latency time of two days. In adrenal medulla, the rates of cyclic AMP accumulation elicited by reserpine, carbamylcholine and theophylline correlate with the increase of tyrosine hydroxylase activity elicited by these drugs. In adrenal medulla, the extent of the increase of cyclic AMP concentrations elicited by the three drugs does not appear related to their ability of increasing tyrosine hydroxylase activity. 11 references. (Author abstract modified)

118747 Ziegler, H.; del Basso, P.; Longo, V.G. Laboratori di Chimica Terapeutica, Istituto Superiore di Sanita, Rome Influence of 6-hydroxydopamine and of alpha-methyl-p-tyrosine on the effects of some centrally acting agents. *Physiology & Behavior.* 8(3):391-396, 1972.

The central effects of morphine, cocaine, phenidylate and chlorpromazine were studied in

300 mice treated with intracerebral injections of 6-hydroxydopamine (6lOHDA). The response to morphine and phenidylate of the animals pretreated with 6-OHDA consisted only of local stereotypies, while the response to cocaine was almost completely blocked. Mice receiving 250 mg/kg i.p.of alpha-methyl-p-tyrosine (alpha-MT) reacted to morphine and amphetamine only with a very slight increase of motor activity. The excitation induced in eight adult cats by morphine was prevented by previous treatment with alpha-MT. 16 references. (Author abstract modified)

118755 Khanna, S.; Nayar, U.; Anand, B.K. Department of Physiology, All-India Institute of Medical Sciences, New Delhi, India Effect of fenfluramine on the single neuron activities of the hypothalamic feeding centers. ***Physiology & Behavior.*** **8(3):453-456, 1972.**

Electrical activity of single neurons of the hypothalamic satiety and feeding centers and other adjacent areas was recorded in 120 adult cats by means of stereotaxically guided steel microelectrodes, before and after fenfluramine infusion in doses of 1.5mg/kg body weight. In addition arterial and venous blood glucose estimations were carried out to assess the levels of glucose utilization. The spike frequency of satiety center units increased while that of feeding center units decreased, in response to fenfluramine while other hypothalamic units did not show any changes. The A-V glucose differences also increased showing increased level of glucose utilization. The significance of these findings in explaining the effects of fenfluramine in depressing appetite have been discussed. 17 references. (Author abstract)

118767 Nance, Dwight M.; Kilbey, M.Marlyne. Worcester Foundation for Experimental Biology, 222 Maple Avenue, Shrewsbury, MA 01545 Self-selection of 5-hydroxytryptophan in dl-para-chlorophenylalanine treated rats. ***Physiology & Behavior.*** **8(3):545-547, 1972.**

Male Sprague-Dawley rats were depleted of serotonin (5-HT) by i.p.injections of dl-para-chlorophenylalanine (p-CPA). In a 36 hour 2 bottle preference test, animals were allowed to choose between distilled water (H2O) and a solution of free base 5-hydroxytryptophan (5-HTP), a precursor of 5-HT. The p-CPA treated animals showed significantly greater preference for the 5-HTP solution than the control animals. A significant increase in brain levels of 5-HT was found for the 5-HT deficient group following consumption of 5-HTP. 12 references. (Author abstract)

118798 Jonsson, G.; Malmfors, T.; Sachs, Ch. Department of Histology, Karolinska Institutet, S-104 01 Stockholm, Sweden Effect's of drugs on the 6-hydroxydopamine induced degeneration of adrenergic nerves. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(3):543-556, 1972.**

The effect of certain drugs (known to affect catecholamine uptake - storage mechanisms) on the 6-hydroxydopamine induced degeneration of adrenergic nerves has been investigated in mouse atrium and iris. The degenerative effect of 6-hydroxydopamine was evaluated by analyzing the changes in H3-amine (H3-noradrenaline or H3-metaraminol) uptake, noradrenaline content and nerve density. Inhibition of monoamine oxidase caused a potentiation, whereas amphetamine could partially counteract the degenerative effect of 6-hydroxydopamine. Bretylium did not interfere with the neurotoxic effect of 6-hydroxydopamine, although a delay in noradrenaline depletion could be observed. Reserpine given either before or after 6-hydroxydopamine produced only minute changes in the action of 6-hydroxydopamine. 29 references. (Author abstract)

118800 Ayhan, I.H. Sct.Hans Hospital, Department E, 4000 Roskilde, Denmark Effect of 6-hydroxydopamine on morphine analgesia. ***Psychopharmacologia (Berlin).*** **25(2):183-188, 1972.**

The influence of 6-hydroxydopamine (6-OHDA) on morphine analgesia estimated by the hot plate method was investigated in rats. When 6-OHDA was injected intraventricularly at a dose of 250 micrograms/rat, it significantly and specifically depleted catecholamines from the brain. Morphine (7.5mg/kg) produced a prominent analgesia in untreated and sham - injected rats whilst the reaction times of 6-OHDA pretreated rats did not change. When L-DOPA (50mg/kg) was given to 6-OHDA pretreated rats, morphine recovered its analgesic action. These results suggest that catecholamines play an important role in morphine analgesia. 28 references. (Author abstract)

04 MECHANISM OF ACTION: BEHAVIORAL

108125 Gardner, Eliot L.; Glick, Stanley D.; Jarvik, Murray E. Albert Einstein College of

Medicine, New York, N.Y. ECS dissociation of learning and one-way cross-dissociation with physostigmine and scopolamine. ***Physiology and Behavior.*** **8(1):11-15, 1972.**

Electroconvulsive shock (ECS) dissociation of learning in mice was studied. Mice were trained on a 1 trial passive avoidance task and retested for retention 24 hr later. ECS administered 25 min before training or 25 min before retest significantly impaired retention, but ECS administered before both training and retest produced no impairment. These results suggest an ECS induced state dependent learning phenomenon. No such state dependency was found when the training retest interval was lengthened to 72 hr and ECS administered 24 hr before training and retest. Physostigmine administered before retest showed state dependency with ECS administered before training while scopolamine administered before training showed state dependency with ECS administered before retest. 12 references. (Author abstract modified)

108131 Eichelman, Burr S., Jr.; Thoa, Nguyen B.; Ng, K.Y. Div.of Clinical and Behavioral Research, NIMH, 9000 Rockville Pike, Bethesda, Md.20014 Facilitated aggression in the rat following 6-hydroxydopamine administration. ***Physiology and Behavior.*** **8(1):1-3, 1972.**

Three to 4 days following a single intracisternal injection (200 micrograms) of 6-hydroxydopamine hydrobromide (6-OHDA) there is a marked and persistent increase (400%) in the number of attacks occurring during shock induced fighting in male Sprague-Dawley rats 60-70 days old. This attack increase appears to correspond with 6-0HDA's effect of depleting brain dopamine (DA) and norepinephrine (NE) and the degeneration of DA and NE terminals. A subsequent dose of 6-OHDA (200 micrograms) increases attack rates still further. There is no significant difference in jump thresholds or mouse killing between 6-OHDA rats and controls. 17 references. (Author abstract)

110975 Hablitz, John J.; Braud, William G. Dept.of Psychology, Univ.of Houston, Houston, Tex. 77004 Adrenalin, sodium amobarbital, and the Kamin effect in the albino rat. ***Learning and Motivation.*** **3(1):51-58, 1972.**

Studies were conducted to determine (1) the form of the retention curve for an incompletely learned appetitive task, and (2) the effect of adrenalin and sodium amobarbital on the 'Kamin effect.'In Expt.1, rats were tested for retention of an appetitively motivated approach response, and Expt.2investigated the retention of an approach - avoidance spatial conflict. No Kamin effect was observed in Expt.1. The saline controls of Expt.2demonstrated a reliable Kamin effect, and adrenalin and sodium amobarbital, administered prior to retention testing, reliably increased and decreased, respectively, the behavorial indices of fear, and abolished the Kamin effect. The results are interpreted as demonstrating that fear initially decreases over time. Some suggestions as to the mechanism of this effect are offered. 14 references. (Author abstract)

111171 Gallup, Gordon G., Jr.; Rosen, Timothy S.; Brown, Charles W. Department of Psychology, Tulane University, New Orleans, Louisiana 70118 Effect of conditioned fear on tonic immobility in domestic chickens. ***Journal of Comparative & Physiological Psychology.*** **78(1):22-25, 1972.**

Young chickens given brief exposure to a compound stimulus which had been previously paired with intense electric shock remained immobile significantly longer following manual restraint than birds which received either shock only or the compound stimulus during training. In a second experiment, the administration of a tranquilizer (metoserpate HCl) reduced the effects of conditioned fear on the resulting duration of immobility. The results provide strong support for the notion that fear underlies the tonic immobility reaction in domestic fowl. 8 references. (Author abstract modified)

111236 Costall, B.; Naylor, R.J. Postgraduate School of Studies in Pharmacology, University of Bradford, Bradford, Yorkshire, England Modification of amphetamine effects by intracerebrally administered anticholinergic agents. ***Life Sciences.*** **11(5):239-253, 1972.**

A combination of peripheral and central injection techniques, was used to investigate the postulate that cholinergic systems in the basal ganglia are important in the control of amphetamine stereotypy and, further, that this control is mediated via a reciprocal balance with dopaminergic systems in the same brain area. In rats, the intensity of stereotyped behavior observed after peripherally administered amphetamine was increased immediately following the injection of orphenadrine into either the striatum or globus

pallidus. However, similar intracerebral injections of atropine and phenglutarimide only potentiated amphetamine stereotypy after a latency of at least 30 mins.,during which time the intensity of stereotypy was markedly reduced. It would therefore appear that cholinergic mechanisms in both the striatum and pallidum are involved in the control of amphetamine stereotypy, but that the nature of this control may not be as simple as may be explained in terms of a reciprocal balance with dopaminergic systems in the same brain areas. The possibility is discussed that actions of drugs other than those that are observed after peripheral administration may be apparent when the drugs are applied directly on to neuronal tissue. 22 references. (Author abstract modified)

111512 Marczynski, T.J. Dept.of Pharmacology, University of Illinois at the Medical Center, Chicago, Ill. 60680 Lysergic acid diethylamide (LSD-25) mimicks the effect of diffuse light input on EEG correlates of conditioned operant behavior in cats. ***Experimental Neurology.*** **34(2):255-263, 1972.**

Cats deprived of food and trained to press a lever for a milk reward, displayed postreinforcement EEG synchronization (PRS) associated with epicortical steady potential shift, reward contingent positive variation (RCPV) over the striate and parastriate cortex. Both phenomena depend on the input of diffuse light, even in subjects trained to perform in darkness. LSD-25 (15-30micrograms/kg,im) restored the PRS-RCPV phenomena in total darkness. Pentobarbital (0.8-1mg/kg, im) was ineffective although it significantly enhanced the PRS-RCPV responses in the presence of light. Some animals were more sensitive than others to LSD-25, and after administration of 20-30micrograms/kg intramuscularly, showed dissociation between the EEG patterns and rewarded lever pressing performance, which was particularly striking in the presence of ambient light. 25 references. (Author abstract)

111827 Sparber, Sheldon B. Dept.of Pharmacology, University of Minnesota, Minneapolis, Minnesota Effects of drugs on the biochemical and behavioral responses of developing organisms. ***Federation Proceedings.*** **31(1):74-80, 1972.**

The action of reserpine on the developing chick embryo was investigated. Reserpine injected prior to incubation was found to decrease hatchability and shift the duration of the incubation curve to the right. In studies of bidirectional avoidance response by young chicks injected prior to incubation, initial rates of avoidance behavior during daily sessions of 17 trials (except at 2 days of age; 10 trials) did not differ. Within 3 days, however, the difference between initial rates of avoidance and third session rates became significant with controls performing better than experimentals. At 7 days of age, after a session in the shuttlebox, the chicks were killed and the brainstems were analyzed for epinephrine and norepinephrine. The reserpine treated group was significantly lower than controls, suggesting that reserpine could have affected the reactivity of the chicks to stress. Data also indicated that the young chick can react to stress with increases in epinephrine and norepinephrine and an increase in serotonin levels within the central nervous system. However, the tissue of reserpine treated chicks cannot bind the norepinephrine-3H after it gains entrance to the brain. Detour responding tasks instituted at 7 days of age compared the higher dose group (0.1mg/kg) with controls. The superior performance of the controls (shorter detour latencies) was significant at the third trial. Flourescence readings at 18 days of age were variable, implying an overshoot or rebound effect at this stage. 40 references.

112066 McDonough, J.M., Jr.; Manning, F.J.; Elsmore, T.F. Department of Experimental Psychology, Walter Reed Army Institute of Research, Washington, D.C. 20012 Reduction of predatory aggression of rats following administration of delta-9-tetrahydrocannabinol. ***Life Sciences.*** **11(3):103-111, 1971.**

Twenty rats were individually tested for the occurrence of an attack upon a turtle 1, 2, 4, and 8 hours after intraperitoneal injections of either placebo or a 6.4mg/kg dose of delta 9-tetrahydrocannabinol (delta-9-THC). In comparison to days when the rat received placebo injections, the percentage of attacks at 1 and 2 hours postinjection was significantly less on days when the delta-9-THC was administered, while at 4 and 8 hours postinjection there was no significant difference between the percentage of attacks on either drug or placebo days. The data support previous research that shows that under certain conditions delta-9-THC has the effect of reducing aggressive behavior. 12 references. (Author abstract modified)

112174 Weiss, Bernard; Gott, C.Thomas. Dept.of Radiation Biology and Biophysics, The University of Rochester Medical Center, 430 Elmwood Ave., Rochester, N.Y. 14642 A microanalysis of drug effects on fixed-ratio performance in pigeons. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(2):189-202, 1972.**

Pigeons trained to peck a lighted key on a fixed ratio 30(FR 30) schedule of food presentation received various dose levels of dl-amphetamine sulfate, sodium pentobarbital, or imipramine hydrochloride. Performance was gauged in terms of the 30 interresponse times (IRTs) within the ratio. The first IRT of the ratio, the time between reinforcement and the first response, increased in a dose related fashion after amphetamine and imipramine and decreased after pentobarbital. The subsequent IRTs displayed similar alterations after these drugs, but the magnitude of the effect depended, in part, on ordinal position within the ratio. Further analyses revealed that changes in the incidence of IRTs greater than one second ('outliers') correlated closely with the mean IRT changes, leading to the hypothesis that drugs mainly act on the cohesiveness of the FR pattern. Changes in the character of the interval histograms revealed further, more subtle alterations, which could be viewed as springing from changes in response topography. 22 references. (Author abstract)

112889 Conrad, Donald G.; Elsmore, Timothy F.; Sodetz, Frank J. Department of Experimental Psychology, Walter Reed Army Institute of Research, Washington, D.C. 20012 Delta-9-tetrahydrocannabinol: dose-related effects on timing behavior in chimpanzee. ***Science.*** **175(4021):547-550, 1972.**

Dose related effects of delta-9-tetrahydrocannabinol on the timing behavior of the chimpanzee were studied. The drug, at doses within the effective range for humans, was administered orally to chimpanzees with stable, efficient timing performances maintained by multilink chained schedules of food reinforcement. Reinforcements decreased with increasing dose, because of decreased frequencies of total operant timing responses and decreased accuracy of the timing performances which did occur. Higher doses exerted an effect for up to 3 days. 13 references. (Author abstract modified)

112917 Baisden, Ronald H.; Isaacson, Robert L.; Woodruff, Michael L.; Van Hartesveldt, Carol. Department of Psychology, University of Florida, Gainesville, Florida 32601 The effect of physostigmine on spontaneous alternation in infant rabbits. ***Psychonomic Science.*** **26(5):287-288, 1972.**

Beginning about 10 days after birth, infant rabbits were tested for spontaneous alternation while under single dosages of physostigmine and dl-amphetamine, as well as after saline injections or without any injection. Only under physostigmine did the animals alternate at levels which were above chance and which approximated levels found in normal adult animals of other species. This indicates that the capacity for spontaneous alternation exists in the infant rabbit, even though it is normally not expressed in behavior. 7 references. (Journal abstract)

112918 Carey, Robert J.; Kritkausky, R.Peter. Veterans Administration Hospital, Syracuse, New York 12310 Absence of a response-rate-dependent effect of d-amphetamine on a DRL schedule when reinforcement is signaled. ***Psychonomic Science.*** **26(5):285-286, 1972.**

In 2 experiments with rats, the effect of a 1mg/kg dose of d-amphetamine on operant responding for water on a differential reinforcement of low rate 22 sec schedule was investigated. If the water reinforcement was signaled by a change in illumination, this dose of amphetamine did not affect response or reinforcement rate. In the absence of an external stimulus correlated with reinforcement, however, amphetamine markedly increased response rate and decreased reinforcement rate on this schedule. Timing behavior was disrupted regardless of whether reinforcement was signaled or nonsignaled. 5 references. (Journal abstract modified)

112926 Eliasson, Mona; Kornetsky, Conan. University of Uppsala, Uppsala, Sweden Interaction effects of chlorpromazine and reticular stimulation on visual attention behavior in rats. ***Psychonomic Science.*** **26(5):261-262, 1972.**

The effects of electrical stimulation of the reticular formation and of chlorpromazine on a visual attention task in the rat were studied. Stimulation at low intensities tended to improve the performance of the animals; however, at higher intensities of stimulation or after chlorpromazine, performance was significantly im-

paired. Chlorpromazine given with stimulation resulted in performance levels not different from that seen after saline alone. In one animal in which electrodes were not in the reticular formation, chlorpromazine did not reverse the effects of stimulation. These results support the hypothesis that the arousal reducing properties of chlorpromazine are mediated by its action on the reticular formation. 5 references. (Journal abstract)

113167 Hitchens, John T.; Orzechowski, Raymond; Goldstein, Sidney; Shemano, Irving. Wyeth Laboratories, Radnor, PA Pharmacologic evaluation of aletamine (alpha-allylphenethylamine hydrochloride) as an antidepressant. *Toxicology and Applied Pharmacology.* 21(3):302-314, 1972.

The pharmacologic activity profile of aletamine closely resembles that of the tricyclic antidepressants imipramine and amitriptyline. Effects shared are antagonism of RO4-1284 induced ptosis and depressed exploratory behavior, depression of spontaneous motor activity, prolongation of hexobarbital hypnosis and anticonvulsant action in mice, hypotension and potentiation of norepinephrine pressor effects in dogs, antimuricidal effects, hypothermia in rats and local anesthesia in rabbits and guinea pigs. Aletamine differed from imipramine and amitriptyline in several ways which are discussed. The effects of aletamine on spontaneous motor activity, hexobarbital hypnosis and body temperature in rodents and on blood pressure in dogs are in opposite direction to those of amphetamine. In further contrast to amphetamine, grouping of mice has no influence on the toxicity of aletamine. Aletamine does not appear to be an inhibitor of monoamine oxidase in vivo since it does not enhance tryptamine-induced convulsions in rats. On an empirical basis, the results indicate that aletamine has pharmacologic properties consistent with potential clinical utility as an antidepressant drug. 30 references. (Author abstract modified)

113363 McKenzie, G.M. Department of Pharmacology, Burroughs Wellcome Company, 3030 Cornwallis Road, Research Triangle Park, N.C. 27709 Role of the tuberculum olfactorium in stereotyped behavior induced by apomorphine in the rat. *Psychopharmacologia (Berlin).* 23(3):212-219, 1972.

Bilateral ablation of the tuberculum olfactorium markedly reduced stereotyped behavior following apomorphine treatment in the rat. Bilateral dissection of the olfactory bulb or large bilateral lesions in the nucleus caudatus putamen did not significantly affect the stereotyped behavior. It is concluded that an intact tuberculum olfactorium is essential for the induction of stereotyped behavior by apomorphine. 16 references. (Author abstract modified)

113364 Larsson, Knut; Komisaruk, Barry R. Rutgers - The State University, Institute of Animal Behavior, 101 Warren Street, Newark, N.J. 07102 Abnormally fast vibrissa movements induced by tetrabenazine in rats. *Psychopharmacologia (Berlin).* 23(3):300-304, 1972.

During exploratory behavior, rats normally display large amplitude, sweeping movements of the vibrissae in regular rhythm of about 7 sweeps per second. Tetrabenazine (a monoamine depleting agent), in a dosage of 10mg/kg, induced abnormal high frequency, low amplitude movements (buzzing) in the vibrissae. This behavioral effect was quantified by high speed motion picture analysis. 10 references. (Author abstract)

113366 Ott, T.; Lossner, B.; Matthies, H. Medizinische Akademie Magdeburg, Institut fur Pharmakologie und Toxikologie, DDR-301 Magdeburg, Leipziger Strasse 44 /The effect of nucleotid-monophosphates on the acquisition and extinction of conditioned reactions./ Die Wirkung von Nucleotid-Monophosphaten auf die Akquisition und Extinktion bedingter Reaktionen. *Psychopharmacologia (Berlin).* 23(3):261-271, 1972.

The acquisition of an optical discrimination reaction in rats is not significantly influenced by intraventricular injection of the nucleotide monophosphates uridine monophosphate (UMP), cytidine monophosphate (CMP), adenosine monophosphate (AMP), guanosine monophosphate (GMP), or thymidine monophosphate (TMP). The extinction, however, is affected differently. A significant delay is found after 100 micrograms UMP or CMP; GMP was only effective after 200 micrograms, AMP was without effect, and TMP enhanced the extinction. The extinction of a different conditioned avoidance reaction was also delayed by UMP or CMP. An injection of UMP, CMP, AMP, or GMP increased the number of positive reactions during the first days of extinction. It is concluded that an

increased supply of pyrimidine nucleotides is of significance for the consolidation of an acquired type of behavior presumably through (RNA) synthesis and its role in the protein synthesis in the nerve cells. 27 references. (Author abstract modified)

113368 Przegalinski, Edmund; Kleinrok, Zdzislaw. Department of Pharmacology, School of Medicine, Jaczewskiego 8, Lublin, Poland An analysis of DOPA-induced locomotor stimulation in mice with inhibited extracerebral decarboxylase. ***Psychopharmacologia (Berlin).*** **23(3):279-288, 1972.**

The effect of different drugs and chemical substances on the strong locomotor stimulation or slight hyperactivity induced by 150 or 100mg/kg of 3,4-dihydroxyphenylalanine, respectively, in mice pretreated with seryl-trihydroxy-benzylhydrazine, an inhibitor of extracerebral decarboxylase was investigated. Results suggest the importance of catecholamines for behavioral stimulation induced in this way and do not confirm the hypothesis proposed by Scheckel et al.(1969) based on conditioned avoidance procedures in rats. The role of dopamine, noradrenaline and 5-hydroxytryptamine is also discussed. 17 references. (Author abstract modified)

113370 Drew, Wm.G.; Miller, Loren L.; Wikler, A. Laboratories of Behavioral Neurophysiology, Dept.of Psychiatry, University of Kentucky Medical Center, Lexington, Ky. 40506 Effect of delta9-THC on the open-field activity of the rat. ***Psychopharmacologia (Berlin).*** **23(3):289-299, 1972.**

Using the open field activity of the hooded rat as a model of overall activity, the dose - response and time - action effects of doses of delta9-tetrahydrocannabinol (delta9-THC) which did not adversely affect spontaneous activity or behavior on appetitively motivated tasks were studied. Subjects received 2 exposures to an open field 1 week apart. Prior to the first exposure subjects were treated with small doses of Tween 80-water. At 30 min or 3 h prior to the second exposure subjects were treated with Tween or delta9-THC in doses which ranged from 0.5-5mg/kg. Results indicated that delta9-THC affected various indices of open field activity such as grooming, sniffing and ambulation differently depending on the time after injection. Rearing and defecation were affected similarly by THC independent of postinjection intervals. 12 references. (Author abstract)

113371 Sparber, S.B.; Tilson, H.A. Department of Pharmacology, University of Minnesota, 105 Millard Hall, Minneapolis, Minnesota 55455 Tolerance and cross-tolerance to mescaline and amphetamine as a function of central peripheral administration. ***Psychopharmacologia (Berlin).*** **23(3):220-230, 1972.**

Differences in tolerance and cross-tolerance to the behavioral effects of d-amphetamine sulfate and mescaline hydrochloride were studied in rats as a function of intraventricular or intraperitoneal routes of administration. Operant behavior, using a fixed ratio schedule of food reinforcement, was the behavioral variable. Following tolerance to d-amphetamine infused intraventricularly, an approximately equipotent dose of mescaline, similarly administered the next day, resulted in behavioral disruption indicating a lack of cross-tolerance. However, following tolerance to mescaline administered intraventricularly, an equipotent dose of d-amphetamine infused the next day did not result in behavioral disruption, indicating cross-tolerance. When d-amphetamine (1.6or 2.5mg/kg) and mescaline (10mg/kg) were administered peripherally (i.p.), no cross-tolerance was found, regardless of the order of drug presentation. Finally, tolerance to amphetamine administered intraventricularly was not indiative of tolerance to amphetamine given intraperitoneally. The next day (after central tolerance) amphetamine disrupted the operant to an equal or greater extent than it had prior to central tolerance formation. This is further evidence that drugs administered directly into the CNS may not be producing their behavioral effects in the same manner as they do via peripheral administration. 19 references. (Author abstract)

113373 Domino, Edward F.; Olds, Marianne E. Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48104 Effects of d-amphetamine, scopolamine, chlordiazepoxide and diphenylhydantoin on self-stimulation behavior and brain acetylcholine. ***Psychopharmacologia (Berlin).*** **23(1):1-16, 1972.**

The effects of d-amphetamine (0.25-8), scopolamine (0.25-8), chlordiazepoxide (2.5-40), and diphenylhydantoin (25-75), given i.p.or s.c.on a mg/kg basis, were studied on self-stimulation behavior in the male albino rat. The dose - effect relationships, the role of baseline rates of responding and their effects on brain acetylcholine (ACh) were determined in rats trained to self-stimulate for electrical reward in

the lateral posterior hypothalamus. The effects of d-amphetamine were both dose and baseline rate dependent. Low-moderate doses (0.5-2.0mg/kg inclusive) facilitated self-stimulation and larger doses (2.0to 8.0mg/kg) depressed responding. The effects of scopolamine in a wide range of dosage were less consistent. A small dose (0.5mg/kg) facilitated only transiently self-stimulation and larger doses (1-8mg/kg) tended to depress this behavior. The effects of chlordiazepoxide were dose dependent. A dose of (5mg/kg) caused facilitation but larger doses (10-40mg/kg) produced depression of self-stimulation irrespective of baseline rates. However, high-rate stimulators showed the most dramatic increases with 5mg/kg of chlordiazepoxide. In contrast, diphenylhydantoin (25-75mg/kg) usually depressed self-stimulation. Low rate self-stimulators showed the most marked depressant effects. Brain ACh was progressively reduced by handling of naive animals, injection of saline, and 1/2h of self-stimulation and escape behavior. Animals not allowed to self-stimulate but given d-amphetamine (2.0mg/kg), scopolamine (2.0mg/kg) showed a significant decrease in brain ACh. Self-stimulation, in addition to medication with the various drugs showed a trend for further reduction in brain ACh but the differences were not statistically significant. 20 references. (Author abstract modified)

113379 Hoffmeister, F.; Schlichting, U.U. Institut fur Pharmakologie der Farbenfabriken Bayer AG, Wuppertal-Elberfeld, Germany Reinforcing properties of some opiates and opioids in rhesus monkeys with histories of cocaine and codeine self-administration *Psychopharmacologia (Berlin).* 23(1):55-74, 1972.

Rhesus monkeys were conditioned to press a key to self-administer intravenous injections of either cocaine (8 monkeys) or codeine (7 monkeys). Every tenth lever press resulted in an injection of 50mcg/kg/inj.cocaine or codeine during daily 3h sessions. Equal doses of cocaine and codeine generated regular comparable rates of self-administration responding. After responding stabilized, different narcotic and nonnarcotic analgesics (morphine, codeine, detropropoxyphene, propiramfumarate, pentazocine and nalorphine) were substituted for cocaine or codeine. At appropriate doses all drugs except for nalorphine, maintained self-administration responding. Monkeys with a codeine self-administration history self-administered higher numbers of injections and showed less intraindividual variability than monkeys with a cocaine self-administration history. 13 references. (Author abstract)

113380 Goldberg, M.E.; Sledge, K.; Robichaud, R.C.; Dubrinsky, B. Warner-Lambert Research Institute, Div.of Biological Research, 201 Tabor Road, Morris Plains, N.J. 07950 A comparative study of the behavioral effects of scopolamine and 4-(1-naphthylvinyl) pyridine hydrochloride (NVP), an inhibitor of choline acetyltransferase. *Psychopharmacologia (Berlin).* 23(1):34-47, 1972.

A selective inhibitor of choline acetyltransferase, 4-(1-naphthylvinyl) pyridine hydrochloride (NVP), was compared with a central cholinergic antagonist, scopolamine, in a number of behavioral procedures in rats. Scopolamine (1mg/kg,i.p.)caused alterations in performance of animals trained on nondiscriminated avoidance, punishment discrimination and conditioned suppression behavior, and had no effect on discrete avoidance behavior after doses as high as 8mg/kg. After nonataxic doses (10-50mg/kg,i.p.), NVP had no inhibitory effects in these behavioral schedules, and only after higher doses (100-200mg/kg,i.p.)was an inhibitory effect on discrete avoidance obtained. It was suggested that less than complete inhibition of choline acetyltransferase does not provide sufficient attenuation of central cholinergic function to mimic the behavioral effects of a cholinergic antagonist. NVP was found to potentiate the pharmacological effects of chlorpromazine and physostigmine, suggesting an inhibitory action on drug metabolizing enzymes; it also had a protective effect upon maximal electroshock seizures in mice. 35 references. (Author abstract)

113381 Dismukes, R.K.; Rake, A.V. Biophysics Department, Pennsylvania State University, University Park, Pa. 16802 Involvement of biogenic amines in memory formation. *Psychopharmacologia (Berlin).* 23(1):17-25, 1972.

Drugs that deplete the biogenic amines of the central nervous system were found to impair the consolidation of memory, in mice, of an avoidance task. Results indicate that normal levels of one of the catecholamines are necessary for the formation of long-term memory. 11 references. (Author abstract)

113457 Gupta, B.D.; Holland, H.C. Dept.of Physiology, S.M.S.Medical College, Jaipur, India

Emotion as a determinant of the effects of drugs and their combination on different components of behaviour in rats. ***Neuropharmacology (Oxford).*** **11(1):31-38, 1972.**

A sample of 48 rats at 2 differing levels of emotionality were subjected to tests of rearing, open field ambulation and escape avoidance conditioning, under doses of amphetamine, methylpentynol and their combination. Analysis of scores under the various treatments indicated that the combined treatment facilitated the simpler activities but did not have a comparable effect on conditioning. A complex interaction between treatment and strain (emotionality) and between treatment, strain and dose emerged and is discussed in detail. 29 references. (Author abstract)

113461 Schallek, W.; Kuehn, A.; Kovacs, J. Pharmacology Dept., Research Div., Hoffmann-La Roche Inc., Nutley, N.J. 07110 Effects of chlordiazepoxide hydrochloride on discrimination responses and sleep cycles in cats. ***Neuropharmacology (Oxford).*** **11(1):69-79, 1972.**

Two series of tests were conducted on freely moving cats with chronically implanted electrodes. In a conditioned discrimination experiment, chlordiazepoxide hydrochloride (10mg/kg p.o.)significantly increased response to the nonrewarded but not to the rewarded signal. Chlorpromazine (5mg/kg p.o.)reduced response to the rewarded signal; phenobarbital (40mg/kg p.o.)had no effect. The electrocorticogram was transmitted by telemetry during these trials. Its frequency was increased by chlordiazepoxide hydrochloride but not by the other drugs. Sleep tests were made with a 6 hr observation period. During acute treatment with the drugs and doses listed above, cats spent less time asleep after chlordiazepoxide hydrochloride than after chlorpromazine or phenobarbital. During chronic treatment with chlordiazepoxide hydrochloride, sleeping time was significantly reduced on the first day of drug administration and increased on the second and fourth. The results are discussed in terms of a disinhibition effect following acute administration of chlordiazepoxide hydrochloride, with possible changes in metabolism or accumulation of metabolites occurring during chronic administration of the drug. 22 references. (Author abstract)

113462 Naylor, R.J.; Olley, Jean E. Postgraduate School of Studies in Pharmacology, Univ.of Bradford, Bradford Modification of the behavioral changes induced by haloperidol in the rat by lesions in the caudate nucleus, the caudate-putamen and globus pallidus. ***Neuropharmacology (Oxford).*** **11(1):81-89, 1972.**

Bilateral lesions in the caudate nucleus or caudate putamen of the rat markedly reduced the catelepsy whilst having no effect on the modification of spontaneous motor activity caused by haloperidol. Unilateral lesions of the caudate nucleus, caudate putamen or globus pallidus caused similar but lesser effects on the catalepsy and were ineffective against the modification of spontaneous motor activity. Bilateral lesions of the globus pallidus, however, abolished both the catalepsy and the modification of spontaneous motor activity. It is suggested that the globus pallidus may be of more importance in the mediation of neuroleptic effects than has previously been considered. 26 references. (Author abstract)

113463 Naylor, R.J.; Olley, Jean E. Postgraduate School of Studies in Pharmacology, Univ.of Bradford, Bradford Modification of the behavioural changes induced by amphetamine in the rat by lesions in the caudate nucleus, the caudate-putamen and globus pallidus. ***Neuropharmacology (Oxford).*** **11(1):91-99, 1972.**

Both unilateral and bilateral lesions of the caudate nucleus, caudate putamen and globus pallidus reduced or abolished the stereotypy normally induced by amphetamine 2.5and 5mg/kg. These doses of amphetamine induced ipsilateral circling in rats with unilateral lesions of the 3 areas and periodic cataleptic behavior in rats with bilateral lesions. No modification of the locomotor stimulant effect of amphetamine was observed in the animals with either unilateral or bilateral lesions of the caudate nucleus and caudate putamen. Animals with bilateral lesions of the globus pallidus, however, exhibited an increased sensitivity to this effect. The effects of the various lesions on stereotypy and locomotor activity differentiate between these 2 aspects of behavior induced by amphetamine and suggest that different anatomical sites of action may be involved. 18 references. (Author abstract)

113466 Wong, R.; Lee, S.K. Dept.of Psychology, Univ.of British Columbia, Vancouver 8, Canada Effects of trifluoperazine upon wheel-running activity of rats. ***Neuropharmacology (Oxford).*** **11(1):137-139, 1972.**

The effects of trifluoperazine upon wheel running activity in rats was studied. Rats in group A were injected with 0.9% NaCl solution while those in group B received trifluoperazine. Six hours later, these injected animals from both groups were placed in individual activity wheels and a measure was taken of their activity over a 2 hr period. After each test trial the rats were returned to their home cage and fed. Following 8 test trials the animals were given 5 additional test trials in which the conditions were reversed. Rats in group A received trifluoperazine while those in group B were injected with saline. The results clearly showed that trifluoperazine depressed the motor activity of rats in a running wheel. This effect was demonstrated between independent groups receiving either the drug or the saline injections and was also evident in the immediate decline in running activity when the rats were switched from saline to trifluoperazine injections. 4 references. (Author abstract modified)

113524 Douglas, Robert J.; Scott, David W. Univ.of Washington, Seattle, Wash. 98105 The differential effects of nitrazepam on certain inhibitory and excitatory behaviors. ***Psychonomic Science.*** **26(3):164-166, 1972.**

The differential effects of nitrazepam on certain inhibitory and excitatory behaviors were examined. Nitrazepam, mixed with food, was orally administered to rats in doses of 0, 10, and 50mg/kg. Both doses, but especially the higher one, had obvious arousal reducing effects in most Ss. Paradoxically, however, the 50mg dose produced apparent rage behavior in several rats while seeming to tranquilize or depress the others. At the higher dose, there also was a marked depression in locomotor, postural, or righting behavior. Despite these obvious overall effects, neither dose had any reliable effect on spontaneous alternation, a response highly related to hippocampal damage or malfunction. The results are at least consistent with the idea that the drug alters the function of the amygdala, but they are decidedly in opposition to suggestions in the literature that nitrazepam either inhibits or enhances the function of the hippocampus. 16 references. (Author abstract modified)

113535 Madden, Thomas C., Jr.; Greenough, William T. Univ.of Illinois, Urbana/Champaign, Ill. 61820 Adrenergic and cholinergic drug effects on retention of a discriminated escape. ***Psychonomic Science.*** **26(3):133-134, 1972.**

The adrenergic and cholinergic drug effects on retention of a discriminated escape were examined. Rats were trained in a discriminated Y-maze escape task. At 1, 3, 7, or 28 days after training, an injection of eserine, amphetamine, chlorpromazine, or saline was given and the rats were retrained. Eserine and chlorpromazine animals showed better retention than saline controls, particularly 1 day after training. Amphetamine enhanced retention at 1 day, but performance deteriorated in groups tested at longer intervals. These results do not agree fully with other experiments and suggest that drug induced changes in retention may involve central activation levels as well as retrieval processes. 12 references. (Author abstract modified)

113537 Wiener, Neil I.; Messer, Jon. York University, Downsview, Ontario, Canada Hemicholinium-3 induced amnesia: some temporal properties. ***Psychonomic Science.*** **26(3):129-130, 1972.**

It was hypothesized that if learning is followed by a transient release of ACh which initiates a long-term change, interfering with cholinergic synthesis might not prevent the development of long-term memory but could result in temporarily rendering the memory inaccessible due to presynaptic transmitter depletion. Following 1 trial passive avoidance training, rats were injected via intrahippocampal cannulae with hemicholinium-3 or saline. Hemicholinium-3 injected rates, showed little retention 18, 24, or 30 h later but complete retention after 6 h, 3 days, and 7 days. 12 references. (Author abstract modified)

113539 Masur, Jandira; Martz, Regina Maria Wey. Setor de Psicofarmacologia, Dept.de Bioquimica e Farmacologia, Escola Paulista de Medicina, St.Paul, Brazil Postexposition administration of d-amphetamine impairs the habituation of rats to an open field. ***Psychonomic Science.*** **26(3):167-168, 1972.**

The results of a study designed to detect the suggested aversive effect of amphetamine in an open field arena are presented. Control rats with a high index of defecation and injected with saline immediately after each exposure to an open field arena showed a gradual decrease in defecation (habituation). However, when treated with d-amphetamine, rats with a high index of defecation even after 18 exposures eliminated a number of fecal boluses similar to that of the first exposure, indicating that the drug impaired habituation.

These data support the hypothesis that amphetamine effects may possess aversive properties. 15 references. (Author abstract modified)

113559 Dewsbury, Donald A. Department of Psychology, University of Florida, Gainesville, Florida 32601 Effects of tetrabenazine on the copulatory behavior of male rats. *European Journal of Pharmacology (Amsterdam).* 17(2):221-226, 1972.

The copulatory behavior of 20 male rats was studied in a series of experiments using doses tetrabenazine from 1.0mg/kg to 16.0mg/kg. Most of the animals attained ejaculation at all dose levels. Doses of 1.0, 2.0, and 3.0mg/kg of tetrabenazine profuced little alteration of copulatory behavior. Administration of tetrabenazine, 4.0mg/kg, produced a reduction in the number of mounts without intromission and in the number of intromissions required to attain ejaculation. Similar effects were obtained with tetrabenazine, 5.0mg/kg, in addition to increases in mean interintromission intervals and postejaculatory intervals. An interpretation is offered according to which tetrabenazine, like reserpine, produces 2 independent effects on copulatory behavior. Its specific effect at intermediate doses is to reduce intromission frequency and mount frequency. At higher doses, these effects become mixed with increases in latency measures. The animals appear to be in cataleptic-like state and much behavior is inhibited. These data are consistent with the hypothesis that moderate decreases in brain monoamine levels facilitate copulatory behavior in male rats. 29 references. (Author abstract)

113560 Neto, J.Palermo; Carlini, E.A. Departamento de Bioquimica e Farmacologia, Escola Paulista de Medicina, Rua Botucatu, 862-04023, San Paulo, Brazil Aggressive behaviour elicited in rats by Cannabis sativa: effects of p-chlorophenylalanine and DOPA. *European Journal of Pharmacology (Amsterdam).* 17(2):215-220, 1972.

The influence of p-chlorophenylalanine (PCPA) and dihydroxyphenylalanine (DOPA) on aggressiveness elicited by marihuana in starved rats was studied. PCPA and DOPA potentiated several fold this behavioral manifestation; the potentiation was still greater when the animals received both drugs. On the other hand, PCPA and DOPA alone or in combination, but without marihuana, failed to elicit aggressive behavior in starved rats. Aggressiveness did not appear when rats fed ad libitum were treated with PCPA, DOPA and marihuana. The role played by starvation, PCPA and DOPA on the capability of marihuana to induce aggressive behavior in rats is discussed. 24 references. (Author abstract modified)

113563 Lal, Samarthji; Sourkes, Theodore L. Laboratory of Chemical Neurobiology, Department of Psychiatry, McGill University, Montreal, Quebec, Canada Effect of various chlorpromazine metabolites on amphetamine - induced stereotyped behaviour in the rat. *European Journal of Pharmacology (Amsterdam).* 17(2):283-286, 1972.

The interaction of chlorpromazine or various chlorpromazine derivatives with amphetamine was studied in rats. Chlorpromazine, 50mg/kg, completely inhibited amphetamine induced stereotyped behavior. Similar doses of chlorpromazine-N-oxide, desmonomethylchlorpromazine and 7-hydroxychlorpromazine showed a less marked antagonism to amphetamine induced stereotyped behavior. No antagonism was shown by chlorpromazine sulfoxide, desdimethylchlorpromazine, 6-hydroxychlorpromazine, or 8-hydroxychlorpromazine. Small doses of chlorpromazine, 5-10mg/kg, and doses of 5 or 50mg/kg of all chlorpromazine derivatives tested markedly prolonged the termination time of amphetamine induced stereotyped behavior. 17 references. (Author abstract)

113568 Sethy, Vimala H.; Winter, J.C. Department of Pharmacology, Yale University, School of Medicine, New Haven, Conn. 06510 Effects of yohimbine and mescaline on punished behavior in the rat. *Psychopharmacologia (Berlin).* 23(2):160-166, 1972.

An investigation tested the hypothesis that conditioned aversive stimuli and drugs such as yohimbine and mescaline produce a common state in animals. Rats were trained to press a bar on a multiple schedule of reinforcement in which one component was variable interval 30 sec (food) and the other component was fixed ratio 10 (concurrent food and electric shock). Yohimbine did not have a selective depressant effect on response rate during the punished component. Indeed, punished rates were elevated or near normal when responding in the nonpunished component was decreased to less than 50% of control values. In contrast, mescaline concurrently depressed rates on both components of the schedule. If yohimbine produces an anxiety-like state in animals which is akin to the state engen-

dered by punishment procedures, the effects of punishment and yohimbine should be additive in terms of their depressant effects on lever press responses. No such additivity was observed in this investigation. The present data do not support the assumption that punishment procedures and the administration of yohimbine produce a common state in the rat. No definitive conclusion could be drawn with respect to the actions of mescaline. 14 references. (Author abstract)

113569 Weissman, Albert. Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340 Effects of amphetamine on locomotion in mice pretreated with desmethylimipramine, tetrabenazine or both. ***Psychopharmacologia (Berlin).*** **23(2):152-159, 1972.**

Amphetamine, at intraperitoneal doses of 0.1-3.2mg/kg, significantly depressed the stimulated motor activity caused by combined treatment with desmethylimipramine (DMI) plus tetrabenazine (TBZ) in mice. The mechanism of this depressant effect probably differs from that for amphetamine's stimulant effect in saline pretreated mice, since doses that produced the effects were dissimilar. DMI alone failed to potentiate or prolong amphetamine induced hyperactivity in mice, probably because it did not block the degradation of amphetamine in mice, as it did in rats. TBZ alone did not potentiate, but rather partially blocked the motor stimulation caused by amphetamine. 13 references. (Author abstract modified)

113643 Stern, Warren C.; Hartmann, Ernest L. Worcester Foundation for Experimental Biology, 222 Maple Ave., Shrewsbury, Mass. 01545 Reduced amphetamine lethality following chronic stress. ***Psychopharmacology (Berlin).*** **23(2):167-170, 1972.**

Rats stressed for up to 4 days by desynchronized sleep deprivation or repeated immersions in cold water showed adrenal gland hypertrophy and thymus gland atrophy. These chronically stressed rats survived markedly longer following a high dose of amphetamine than nonstressed rats. However, the usual finding of enhanced amphetamine lethality when a novel acute stress is paired with amphetamine administration (in previously nonstressed rats) was confirmed. 12 references. (Author abstract)

113644 Lehtinen, Paivi; Hyyppa, M.; Lampinen, Pirkko. Department of Anatomy, University of Turku, 20520 Turku 52, Finland Sexual behaviour of adult rats after a single neonatal injection of reserpine. ***Psychopharmacologia (Berlin).*** **23(2):171-179, 1972.**

To investigate whether reserpine given in the critical period of sexual differentiation of the rat brain affects adult sexual behavior, female and male rats were given a single injection of reserpine on the fourth day after birth, and their sexual behavior was tested at maturity. In the 11 consecutive daily tests for spontaneous sexual behavior the reserpine treated female animals showed fewer regular behavioral and vaginal estrous cycles than the control animals. 19% of the reserpinized and none of the control animals had prolonged estrous behavior without a coincident prolonged vaginal cycle. The receptivity quotients of the reserpine treated animals were reduced. In the tests for hormone induced sexual behavior after ovariectomy, no statistically significant differences between the number of animals responding or between the receptivity quotients occurred. The tests for spontaneous sexual behavior in males showed that the reserpinized animals needed fewer intromissions to ejaculate than the controls. The significance of these findings is discussed. 25 references. (Author abstract)

113725 Emley, G.S.; Hutchinson, R.R. Research Dept., Fort Custer State Home, Augusta, Mich. 49012 Basis of behavioral influence of chlorpromazine. ***Life Sciences.*** **11(1):43-47, 1972.**

Squirrel monkeys, studied during response independent, periodic presentation of electric shock, engaged in biting attack behavior after shock and anticipatory manual and locomotor behavior prior to shock. For all subjects, administration of chlorpromazine caused a dose dependent decrease in biting attack reactions and a simultaneous increase in anticipatory manual responses. d-Amphetamine increased while morphine decreased both responses. The results suggest that the tranquilizer, chlorpromazine, produces a shift in an organism's response tendency from postevent aggressivity toward preevent anticipatory responding. 12 references. (Author abstract)

113726 Erickson, Carlton K. Dept.of Pharmacology and Toxicology, School of Pharmacy, Univ. of Kansas, Lawrence, Kan. 66044 Facilitation of discriminated leverpress avoidance learning by ribaminol. ***Life Sciences.*** **11(1):23-32, 1972.**

Ribaminol facilitates discriminated leverpress avoidance learning in the rat when injected im-

mediately before daily training sessions, but does not facilitate learning when injected immediately after daily training sessions. These results, along with a lack of significant spontaneous motor activity stimulation by the drug, point to the suggestion that ribaminol may facilitate learning by enhancing motivation or alertness rather than by stimulating the consolidating neural memory trace or merely stimulating activity. 7 references. (Author abstract modified)

113883 Brebbia, D.Robert; Watson, James M.; Pyne, Evelyn T. Rockland State Hospital Rubidium chloride and the sleep cycle of the rat. ***Psychophysiology.*** **9(1):93-94, 1972.**

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which the effect of rubidium, a monovalent cation, on induction of transitory EEG activation, cortical spiking, motor activity, alertness, and aggressiveness in rats was studied. Implanted animals were monitored continuously for 1 week to obtain baseline patterns for the sleep - wake cycle. Then, single intraperitoneal injections of varying doses of rubidium chloride (RbCl) in saline were administered to test the acute effects of the drug. EEG changes similar to those reported for the monkey were observed. Alterations in the sleep - wake cycle included increased latencies to sleep onset and to first REM period with reduction in total sleep time. The percentage of REM relative to NREM sleep decreased slightly with the lower dose but increased at the highest drug level. The first effect appears related to increased arousals coupled with decreased duration of REM periods within the first 3 hrs; the opposite effect appears to be due to increased NREM interruptions. Notable were shortened REM periods, interrupted by relatively long waking period which shortened the sleep cycle. These effects approximated the time course of Rb cation concentrations in tail vein blood of unimplanted animals injected with the maximum dose. (Journal abstract modified)

113905 Stark, P.; Fuller, R.W. The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206 Behavioral and biochemical effects of p-chlorophenylalanine, 3-chlorotyrosine and 3-chlorotyramine. A proposed mechanism for inhibition of self-stimulation. ***Neuropharmacology (Oxford).*** **11(2):261-272, 1972.**

Rats and dogs, with electrodes chronically implanted in the posterior hypothalamus, pressed a lever to receive electrical stimuli at various current intensities. p-Chlorophenylalanine, a drug that lowers brain serotonin by causing inhibition of tryptophan hydroxylation, inhibited self-stimulation. This inhibition of self-stimulation was not temporally correlated with lowering of brain serotonin. p-Chlorophenylalanine also inhibits phenylalanine hydroxylation, and plasma levels of phenylalanine were increased; there was little change in plasma tyrosine levels. Plasma levels of phenylalanine and of p-chlorophenylalanine did not correlate well with the inhibition of self-stimulation behavior in either species. 3-Chlorotyrosine, a known metabolite of p-chlorophenylalanine in vitro, inhibited self-stimulation in rats at doses lower than those of p-chlorophenylalanine but did not significantly lower brain serotonin. 3-Chlorotyramine, the decarboxylated product of 3-chlorotyrosine, also inhibited self-stimulation. The results suggest that the 3 compounds inhibited self-stimulation by a mechanism independent of brain serotonin. The greater potency of 3-chlorotyrosine raises the possibility that this behavioral effect of p-chlorophenylalanine occurs after it is converted to 3-chlorotyrosine. A possible metabolic pathway that could yield a false neurotransmitter is suggested. 32 references. (Author abstract)

113907 Maickel, R.P.; Webb, R.W. Department of Pharmacology, Medical Sciences Program, Indiana University, Bloomington, Indiana 47401 Taste phenomena and drug effects on thirst-induced fluid consumption by rats. ***Neuropharmacology (Oxford).*** **11(2):283-290, 1972.**

Taste phenomena and drug effects on thirst induced fluid consumption by rats was studied. Rats were trained to consume all of their daily fluid intake in 1 hr period each day. The consummatory volume during this period ranked from greatest to least in the order: 9% sucrose, 0.004%saccharin, distilled water, 0.005% tartaric acid. When various drugs were administered prior to the consummatory sessions, differential effects were observed in molar dose response curves of the various drugs. Amphetamine was most potent against distilled water and totally ineffective against sucrose. Atropine was most effective against saccharin and least effective against tartaric acid. Methapyrilene was most effective against distilled water and least effective against tartaric acid. 22 references. (Author abstract modified)

113977 Nakamura, K.; Thoenen, H. Dept.of Biochemistry and Metabolism, Hoffman-La Roche Inc., Nutley, N.J. Increased irritability: a permanent behavior change induced in the rat by intraventricular administration of 6-hydroxydopamine. *Psychopharmacologia (Berlin).* 24(3):359-372, 1972.

Intraventricular injection of 2 doses of 300 micrograms of 6-hydroxydopamine (6-OHDA) into rats induced an increased reactivity to exogenous (nonpainful) stimuli. This increased irritability lasted more than 4 months (the longest period studied) and consisted of crying, hissing, urination, defecation, standing in an upright posture, biting and panic jumping. The degree of irritability was inversely correlated with the level of brain norephnephrine (NE). The uptake of 3H-NE into all brain regions studied was decreased after administration of 6-OHDA. The rate of 3H-NE decay from the brain stem (hypothalamus, medulla-pons) was delayed 1 week and accelerated 9 weeks after 6-OHDA administration. The decay of 3H-NE from the residual parts of the brain was enhanced both 1 and 9 weeks after 6-OHDA injection. Diazepam, chlordiazepoxide and meprobamate suppressed the increased irritability at doses which did not cause muscle relaxation. The normalization of the behavior produced by diazepam was accompanied by a normalization of the rate of 3H-NE decay both in the brain stem and the residual parts of the brain. The neuroleptics chlorpromazine and haloperidol were effective in abolishing the increased irritability only at strongly sedative doses. 43 references. (Author abstract)

113980 Cools, A.R. Dept.of Pharmacology, Univ.of Nijmegen, Nijmegen, The Netherlands Neurochemical correlates of the waltzing-shaker syndrome in the Varitint-waddler mouse. *Psychopharmacologia (Berlin).* 24(3):384-396, 1972.

In the order to examine activity of the dopamine system in the Varitint-waddler (Va) mouse, behavior effects of haloperidol and dexamphetamine on waltzing Va, nonwaltzing Va and nonmutant mice were investigated. The dopamine system of these mice was studied by macro-autoradiography with 14C-dihydroxyphenylalanine. High doses of haloperidol were similarly effective in both mutant and non mutant mice: they induced a highly characteristic cataleptic effect in all types of mice. Low doses were significantly less effective in the waltzing Va mice: they induced a marked shift from a small increase of the sitting frequency in the waltzing mice to a large increase of this measure in the nonmutant mice. Several behavioral measures of the untreated waltzing mice mimicked those of control mice treated with amphetamine. Amphetamine reversed original strain differences and depressed several stereotyped Va activities. The autoradiograms of the waltzing Va mice, which showed a marked labelling of the Harderian gland, differed significantly from those of the nonwaltzing Va mice and controls, which whowed no labelling of this gland. It is suggested that a hyperactive dopaminergic mechanism is involved in the waltzing-shaker syndrome of the Varitint-waddler. 33 references. (Author abstract)

113982 Schecter, Martin D.; Rosecrans, John A. Dept.of Pharmacology, Univ.of Melbourne, Parkville, Victoria 3052, Australia Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine. *Psychopharmacologia (Berlin).* 24(3):417-429, 1972.

Rats were trained to make a specific behavioral response in a T-maze apparatus conditional upon whether they were injected with 0.4mg/kg nicotine or saline. Depletion of brain levels of 5-hydroxytryptamine by orally administered para-chlorophenylalanine had no significant effect on the rats' ability to discriminate nicotine. However, both insoluble alpha-methyl-p-tyrosine and its ester, at intraperitoneal doses of 90 and 135mg/kg, respectively, significantly descreased discrimination of nicotine at 180 and 270 min postadministration. At these doses and times, saline discrimination was not altered. The experimental evidence indicates that nicotine's central nervous system (CNS) cueing effect is mediated by norephinephrine, and this is discussed in light of the Burn and Rand hypothesis. It is proposed that, nicotine may act on a specific nicotine sensitive cholinergic receptor in the CNS, which causes release of norepinephrine which, in turn, produces the interoceptive cueing effect that enables the rats to make the appropriate behavioral response. 25 references. (Author abstract)

114566 Hartmann, Ernest; Stern, Warren C.; Chung, Richard; Draskoczy, Paul R.; Schildkraut, Joseph J. Boston State Hospital, Boston, Mass. 6-Hydroxydopamine: effects on sleep patterns and on behavior in the rat. *Psychophysiology.* 9(1):85, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which 13 male Sprague-Dawley rats received 6-hydroxydopamine (6HD) 200 micrograms followed by 300 micrograms 72 hours later, injected intracisternally. Thirteen control animals had similar injections of vehicle only. Eleven animals then had electrodes implanted and were employed in 8 and 24 hour sleep studies over a 3 month period. Behavioral studies were done 6 to 12 weeks after injection. One week after 6HD whole brain norepinephrine was 27% of matched control values; 21 weeks after 6HD it was 41%. 6HD rats showed 40%more desynchronized sleep time than controls. There was a slight reduction in W; S - time was unchanged. These results appeared over the entire 3 months of recordings. Basal activity levels were unchanged by 6HD. However, amphetamine (2mg/kg) produced a significant increase in activity of controls but no change in 6HD animals. The 6HD group tended to show poorer active avoidance acquisition. 6HD animals showed significantly higher mean shock induced aggression than controls. The long-term effects on sleep of intrathecal 6HD are remakably similar to the acute effects reported after oral 1-alphamethylparatyrosine. These substances both reduce brain catecholamine levels, but by very different mechanisms. These data are compatible with the view that D - sleep has a role in maintaining catecholaminergic neuronal systems. (Journal abstract modified)

114572 Canales, L.; Harner, R.N.; Hitzig, B. Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa. The effect of MK-486 on behavioral and EEG changes induced by intravenous L-dopa. *Psychophysiology.* 9(1):87, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is noted that MK-486 is a potent aromatic amino acid decarboxylase inhibitor which does not penetrate the blood brain barrier. In an isolation chamber monitored with closed circuit TV, continous EEG recordings were obtained from cats chronically implanted with cortical and depth electrodes. Drugs were given through a 6 ft.intravenous catheter. At the onset of spontaneous slow sleep (SS), 20mg/kg of MK-486 was injected. Each cat continued in SS and 6 had REM period. L-dopa, 5 to 15mg/kg, was administered 30 min later, preceded by test injections of saline. Onset of arousal following 15mg/kg L-dopa occurred after 219.1plus or minus 40.0sec and persisted for 251.0plus or minus 28.0min. This response did not occur in 1 animal at 5mg/kg, but occurred on 2 out of 3 occasions at 7.5mg/kg. Each animal showed periods of immobile posture or hallucinatory behavior. Vomiting and defecation were regular features but severe panting, drooling, and piloerection noted for long periods in previous studies were less pronounced here. It is concluded that MK-486 does not impair EEG arousal and behavioral effects produced by L-dopa. This is further evidence for central action on a previously postulated dopaminergic arousal mechanism. (Journal abstract modified)

114573 Hartman, Ernest; Chung, Richard. Boston State Hospital, Boston, Mass. L-tryptophane: effect on sleep in the normal rat and the rat with lowered brain catecholamines. *Psychophysiology.* 9(1):87-88, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that L-tryptophane was investigated at doses of 300, 450 and 600mg/kg in normal rats and in rats injected intrathecally with 6-OH-dopamine (6HD), 2 injections; free base 200 micrograms followed by 300 micrograms 72 hours later. These rats had brain norepinephrine levels above 40% of normal. A total of 54 8 hour recordings were run in 11 animals. Total time in W(waking), S (synchronized) and D (desynchronized) sleep was not significantly changed. L-tryptophane produced a significant decrease in sleep latency in normal as well as 6HD tested animals. The number of awakenings and number of D-periods (for cycles) were not significantly affected. There was no clear interaction between tryptophane effect and the lowered catecholamine levels. The results after L-trypopthane, reduced sleep latency with maintenancy of sleep architecture, are similar to findings in man, and support previous suggestions that L-tryptophane may hav e some use as a physiological hypnotic.

114577 Masur, Jandira; Karniol, Isac G.; Neto, Joao Palermo. Departamento de Bioquimica e Farmacologia, Escola Paulista de Medicina, Rua Botucatu, 862-04023, Sao Paulo, Brazil Cannabis sativa induces 'winning' behaviour in previously 'loser' rats. *Journal of Pharmacy and Pharmacology (London).* 24(3):262, 1972.

The effects of administration of Cannabis sativa in a social hierarchy established before drug administration was studied in the rat. Twelve 3 month old rats were trained in a contest situation. In the 2 sessions before drug phase, the 6 loser animals had a low frequency of winning behavior but after being given cannabis extract ther e was a marked change in the hierarchy. Cannabis sativia temporarily modified the rat's social behavior. 2 references.

114582 Hartmann, Ernest; Chung, Richard. Sleep and Dream Laboratory, Boston State Hospital, 591 Morton St., Boston, Mass. 02124 Sleep-inducing effects of L-tryptophan. ***Journal of Pharmacy and Pharmacology (London).*** **24(3):252-253, 1972.**

The effects of several dose levels of L-tryptophan on recorded sleep was studied in the rat. It was found that the amino acid, L-tryptophan can produce significant decreases in sleep latency with little change in sleep architecture. This differentiates tryptophan from most clinical hypnotics, which distort sleep architecture considerably. 7 references.

114688 Niemegeers, C.J.E.; Verbruggen, F.J.; Wauquier, A.; Janssen, P.A.J. Janssen Pharmaceutica, Research Laboratoria, B-2340 Beerse, Belgium The influence of haloperidol and amphetamine on two different noise-escape situations in rats. ***Psychopharmacologia (Berlin).*** **25(1):22-31, 1972.**

The learning process of two different noise - escape responses -- lever pressing and jumping -- was studied in the same rats using a shuttle box automatically transformable during the experimental sessions into two Skinner boxes. The effects of different doses of haloperidol and amphetamine were studied in rats overtrained in the two situations. The learning process was slower in the Skinner box than in the shuttle box. To reach the maximum response level in 50% of the rats 13 to 18 training sessions of five min were necessary in the shuttle box versus 31 to 36 in the Skinner box. Haloperidol prolonged the latency (T) and reduced the frequency (F and F') of both lever pressing (L) and jumping responses (J) to about the same extent at the same dose levels. At 0.005mg/kg haloperidol slightly increased F'L. At doses lower than 2.5mg/kg, amphetamine decreased T in both the Skinner and the shuttle box and the ineffective responses (F') were increased up to four to five times their control values. The lowest effective dose was 0.16mg/kg in the shuttle box (F'J) and 0.31mg/kg in the Skinner box (F'L). At 2.5mg/kg amphetamine increased T and reduced F. 6 references. (Author abstract)

114689 Sara, S.J.; Lefevre, D. Center of Experimental and Comparative Psychology, University of Louvain, Pellenberg, Belgium Hypoxia-induced amnesia in one-trial learning and pharmacological protection by Piracetam. ***Psychopharmacologia (Berlin).*** **25(1):32-40, 1972.**

Rats were given Piracetam or saline 30 min orally before one trial passive avoidance training; after training they were submitted to nitrogen induced hypoxia (sudden and progressive procedure) or were confined to the hypoxia cage with a normal atmosphere. Results showed that: hypoxia prevented the avoidance response on day 2 for the saline injected animals and that Piracetam protected the animals from this hypoxia induced amnesia. The results are discussed in terms of electrophysiological and biochemical modifications which have been found to be associated with both hypoxia and Piracetam. 18 references. (Author abstract modified)

114690 Kirkby, Robert J.; Bell, David S.; Preston, Alan C. Department of Psychology, University of Sydney, Sydney, Australia The effects of methylamphetamine on stereotyped behaviour, activity, startle, and orienting responses. ***Psychopharmacologia (Berlin).*** **25(1):41-48, 1972.**

In two experiments the relationships between methylamphetamine induced stereotyped behavior and locomotory activity, startle reactivity, and orienting responsiveness were investigated in laboratory rats. Experiment I showed that administration of 5mg/kg methylamphetamine, compared to 0.5mg/kg methylamphetamine or saline, resulted in increased stereotypy, increased startle reactivity, and decreased orienting. Experiment II confirmed that the higher dose of methylamphetamine enhanced startle reactivity, and indicated that concomitant with this, habituation to successive startle stimuli was inhibited. The similarities between stereotypy in the rat and schizophreniform behavior in the human were discussed. 18 references. (Author abstract)

114691 Bueno, Orlando F.A.; Carlini, E.A. Departamento de Bioquimica e Farmacologia, Escola Paulista de Medicina, Rua Botucatu, 862, 04023 Sao Paulo, Brazil Dissociation of learning in

marihuana tolerant rats. *Psychopharmacologia (Berlin).* 25(1):4956, 1972.

Rats previously trained to climb a rope were injected daily with a marihuana extract; the drug initially impaired the performance but after 14 injections the animals became completely tolerant. The rats were then trained to press either one of the two bars of a Skinner box. On each day only one of the bars was activated to deliver the reward; 45 min before the experiment an injection of cannabis extract (left bar) or of control solution (right bar) was given. After 30 injections the animals learned which bar to press in order to obtain the reward, indicating that they were still using some effect of marihuana as a discriminative stimulus. This dissociation of learning produced in marihuana tolerant rats, (as measured by rope climbing), indicates that tolerance is not complete. Furthermore, as dissociation of learning is not produced by peripheral effects of drugs, it is suggested that even after chronic treatment marihuana continues to act on the central nervous system. 19 references. (Author abstract)

114735 de Oliveira, L.; Graeff, F.G. Dept.of Psychology, Faculty of Philosophy and Sciences, Ribeirao Preto, S.P., Brazil Comparison between the effects of apomorphine and amphetamine on operant behavior. *European Journal of Pharmacology (Amsterdam).* 18(2):159-165, 1972.

Dose effect relationships for apomorphine and amphetamine on lever pressing behavior of rats, maintained by a two min fixed interval schedule of water presentation, were determined. Lower doses of amphetamine increased responding particularly when control baseline rats were low, whereas higher doses decreased responding. In contrast, doses of apomorphine only decreased responding. Chronic reserpine treatment reduced the baseline response rate to approximately 15% of the mean control rate. Certain doses of amphetamine, but not apomorphine, partially antagonized the rate depressant effect of reserpine. Since apomorphine stimulates central dopamine receptors, the results suggest that dopaminergic mechanisms are not significantly involved in the mediation of the rate stimulant effects of amphetamine on operant behavior. 27 references. (Author abstract)

114980 Thoa, N.B.; Eichelman, B.; Ng, K.Y. NIMH, Division of Clinical and Behavioral Research, 9000 Rockville Pike, Bethesda, MD 20014 Aggression in rats treated with dopa and 6-hydroxydopamine. *Journal of Pharmacy and Pharmacology (London).* 24(4):337-338, 1972.

Vigorous spontaneous fighting in rats first treated with intracisternal 6-hydroxydopamine and then given L-Dopa and the peripheral decarboxylase inhibitor, MK-486 (methyldopahydrazine), is reported. These rats also showed a marked rise of the adrenal enzyme, tyrosine hydroxylase. Spontaneous fighting seen in 6-hydroxydopamine treated rats given dopa and MK-486 with or without FLA-63 (bis-4-methyl-1-homopiperazinylthiocarbonyldisulfide), which inhibits dopamine-beta-hydroxylase and, consequently, noradrenaline synthesis, appears to involve a dopaminergic neural system. The necessity of pretreatment with 6-hydroxydopamine to elicit spontaneous fighting suggests that either a denervation hypersensitivity effect occurs with exogenous dopa or dopamine or that 6-hydroxydopamine has functionally destroyed an inhibitory system which blocked the behavioral effect of dopa. 8 references.

115046 Levin, Barry E.; Smith, Gerald P. no address Impaired learning of active avoidance response in rats after lateral hypothalamic injection of 6-hydroxydopamine. *Neurology.* 22(4):433, 1972.

At the 1972 session on behavior of the American Academy of Neurology impaired learning of active avoidance response in rats was noted after lateral hypothalamic injection of 6-hydroxydopamine. Rats were tested in a one-way avoidance shuttle box some time after injections in the lateral hypothalamus (LH) or the posterior LH or the anterior, posterior and medial LH. Data indicates that learning an active avoidance response depends on the integrity of ascending catecholaminergic axons in the lateral hypothalamus of the rat.

115071 Fibiger, H.C.; Lonsbury, B.; Cooper, H.P.; Lytle, L.D. Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, MA 02139 Early behavioural effects of intraventricular administration of 6-hydroxydopamine in rat. *Nature New Biology (London).* 236(68):209-211, 1972.

The period of increased locomotor activity shortly after intraventricular administration of 6-hydroxydopamine in the presence of the monoamine oxidase inhibitor, pargyline, was investigated in rats. Alone, 6-hydroxydopamine

produced a significant decrease in activity; in combination with pargyline pretreatment th e same drug elected pronounced hyperactivity, aphygra and adepsia. Reserpine pretreatment failed to nullify the 6-hydroxydopamine mediated hyperactivity. Results suggest that soon after intraventricular injection, 6-hydroxydopamine has an indirect sympathomimetic effect which depends on the continuous synthesis of catecholamines but which is independent of reserpine sensitive stores of biogenic amines. Results ar e compatible with an amphetamine like action of this drug. Rats, in the absence of pargyline pretreatment, seemed essentially normal 72 h after 6-hydroxydopamine treatment, though their spontaneous activity was depressed and there was a decrease in self-grooming behavior. 20 references.

115077 MacDonnell, M.F.; Fessock, L. Center for Alcohol Studies, Rutgers University, New Brunswick, NJ 08903 Some effects of ethanol, amphetamine, disulfiram and p-CPA on seizing of prey in feline predatory attack and on associated motor pathways. *Quarterly Journal of Studies on Alcohol.* 33(2):437-450, 1972.

Experimental study of the effects of certain chemicals on seizing prey in feline predatory attack and on associated motor pathways is reported. Alcohol and amphetamine depressed the evoked responses during feline predatory attack while disulfiram and p-chlorophenylalanine enhanced them. 21 references. (Journal abstract modified)

115213 Bloomfield, T.M. Dept.of Psychology, York University, Downsview 463, Ontario, Canada Contrast and inhibition in discrimination learning by the pigeon: analysis through drug effects. *Learning and Motivation.* 3(2):162-178, 1972.

Studies of effects of chlorpromazine hydrochloride and desmethylimipramine hydrochloride in learning are reported. In a series of four experiments, pigeons were trained on either an easy, red/green discrimination with or without a penalty for errors, or a more difficult left/right discrimination with 'penalty. Some groups of birds were injected with chlorpromazine or desipramine prior to acquisition sessions or to sessions following learning of the discrimination. Drug injection caused substantial impairment of acquisition or retention of the left/right discrimination alone, whereas in all discriminations the behavioral contrast effect was abolished. The results suggest that inhibition of errors depends upon the difficulty of discrimination and the presence of a penalty procedure, and determines both contrast in the saline injected groups and the extent of impairment in the drug injected groups. 14 references. (Journal abstract)

115585 Horovitz, Zola P.; Beer, Bernard; Clody, Donald E.; Vogel, John R.; Chasin, Mark. Squibb Institute for Medical Research, New Brunswick, NJ Cyclic AMP and anxiety. *Psychosomatics.* 13(2):85-92, 1972.

The relationship between cyclic AMP (adenosine 3', 5'-monophosphate or cyclic adenylate) and anxiety is discussed and results reported of experiments on rats and other animals. Correlations with some behavioral effects of psychotropic agents were made with their measure of cAMP phosphodiesterase activity, because the activity of this enzyme in the brain exceeds that of adenylate cyclase by 100 fold. The experimental condition of anxiety was produced by providing a conflict situation between a thirsty rat's motivation for water associated with unavoidable shock. It was predicted that both dibutyryl cAMP and several other known inhibitors of brain cAMP phosphodiesterase activity would produce an attenuation of the effects of punishment, as measured by the conflict test. Results indicate that: (1) some potent anxiolytic drugs, like diazepam, and chlordiazepoxide are also potent inhibitors of brain cAMP phosphodiesterase activity; (2) dibutyryl cAMP has antianxiety properties; (3) the methylxanthines (caffeine, theophylline, and theobromine), long known as inhibitors of cAMP phosphodiesterase activity, have significant activity in the conflict test, but are not as specific for brain tissue as the antianxiety agents; (4) combinations of theophylline and chlordiazepoxide, or SQ 20,009 and chlordiazepoxide, have at least additive effects in the conflict test; (5) a significant correlation exists between the activity of a drug in the conflict test and its potency in inhibiting brain cAMP phosphodiesterase activity; and (6) IMA, a compound that appears to stimulate cAMP phosphodiesterase activity can antagonize the effects of chlordiazepoxide on the antianxiety procedure. 21 references. (Author abstract modified)

116083 Kesner, Raymond P.; Conner, Hubert S. Center for Advanced Study in the Behavioral

Sciences, Stanford, CA 94305 Independence of short- and long-term memory: a neural system analysis. *Science.* 174(4033):432-434, 1972.

To test for retention at short and long intervals, various neural structures of rats were stimulated after they had an aversive experience. The rats were given electrical stimulation to the midbrain reticular formation or to the hippocampus four seconds after they received shocks contingent on the animals' bar press responses. They were retested for memory of the shocks 64 seconds or 24 hours after the shocks. The animals that received stimulation to the midbrain reticular formation showed anmesia at the 64 second retest and memory at the 24 hour retest. In contrast, animals that received stimulation to the hippocampus showed memory at the 64 second retest and amnesia at the 24 hour retest. The data support a dual, parallel processing model of memory. 13 references. (Author abstract)

116085 Beer, Bernard; Chasin, Mark; Clody, Donald E.; Vogel, John R.; Horovitz, Zola P. Squib Inst.for Medical Research, New Brunswick, NJ 08903 Cyclic adenosine monophosphate phosphodiesterase in brain: effect on anxiety. *Science.* 175(4033):428-430, 1972.

Some behavioral effects of psychotropic agents are correlated with their effects on cyclic (adenosine mohophosphate) phosphodiesterase activity rats, mice, and cats. Results indicate that drugs which reduce anxiety may be mediated by cyclic AMP in the brain because 1) potent anxiety reducting drugs are also potent inhibitors of brain phosphodiesterase activity; 2) dibutyryl cyclic AMP has the ability to reduce anxiety; 3) the methylxanthines show significant anxiety reducing effects; 4) theophylline and chlordiazepoxide produce additive anxiety reducing activity; and 5) there is a significant correlation between the anxiety reducing property of drugs and their ability to inhibit phosphodiesterase activity in the brain. 28 references. (Author abstract)

116228 Houser, Vincent P.; Pare, William P. Veterans Administration Hospital, Perry Point, MD 21902 A method for determining the aversive threshold in the rat using repeated measures: tests with morphine sulfate. *Behavior Research Methods and Instrumentation.* 4(3):135-137, 1972.

A procedure which provides an objective automated technique for the psychophysical assessment of the aversive threshold and allows the animal Ss to serve as their own controls is described. Sensitivity to drug effects, as well as comparisons between drugs, using the same animals are possible also. Using a rectangular tilt cage, the aversive threshold to grid shock was defined as that intensity avoided 75% of the time. Each shock intensity (30, 60, 90, 120, and 150 microA) was presented for five min on one side of the cage and then switched to the other side for five min, thereby forcing the animal to sample each shock intensity. Aversive thresholds were determined daily for each rat. The analgesic effects of morphine sulfate were compared to saline. Animals were tested for three days at each morphine dose level (2, 4, 8, and 16mg/kg). Each three day morphine series alternated with three days of testing under saline. Significant differences were detected between saline and morphine at 4, 8, and 16mg/kg. 11 references. (Author abstract)

116288 Andrew, R.J.; Rogers, L.J. Ethology and Neurophysiology Group, Biology School, University of Sussex, Brighton, England Testosterone, search behaviour and persistence. *Nature (London).* 237(5354):343-346, 1972.

The effect of testosterone on the persistence with which male chicks respond to a particular type of stimulus in search tests is reported. In the search it is clear that pecks at pebbles are carefully avoided, which implies a rigorous use of search specifications, resulting in the avoidance of nonprefered food as well as pebbles. The marked increase in the persistence of search behavior induced by testosterone suggests that the degree of persistence in use of central specifications for stimuli is an independent variable of importance. High persistence of this type can be distinguished from inability to inhibit or withhold responses by the fact that testosterone does not affect the ability to maintain widely spaced responses nor does it affect extinction following nonreinforcement although it does reduce distraction in such situations. 8 references.

116852 Ellinwood, Everett H., Jr.; Sudilovsky, Abraham; Nelson, Linda. Department of Psychiatry, Duke Medical Center, Durham, NC Behavioral analysis of chronic amphetamine intoxication. *Biological Psychiatry.* 4(3):215-230, 1972.

Description and quantification of behavioral analyses of experimental cats subjected to chronic methamphetamine intoxication are reported.

Phenomenological descriptions and recordings on video tape of the ongoing behavior were used in the analysis and construction of indexes of ataxia, dystonic posture, transient and patterned movements, and a multivariate behavioral rating chart. Attention was focused on the dyssynchrony of posture and motility throughout the intoxication period. It is suggested that amphetamine stimulation of various dopamine systems without the coordinating and inhibiting effects of the norepinephrine systems tends to allow individual lower level organizational substrates to become relatively autonomous. 19 references. (Author abstract modified)

117001 Crowley, Terrence P.; Sisemore, David A. University of Southern Mississippi, Hattiesburg, MS 39401 The failure of methamphetamine hydrochloride to produce dissociation of an escape response. ***Psychonomic Science.*** **28(1):50-52, 1972.**

The effect of methamphetamine hydrochloride on the dissociation of an escape response was studied in 27 rats. Rats were trained to make an escape response at one of two dosage levels of methamphetamine or in a placebo state. Subsequently, they were tested in both drug states, as well as in the nondrugged state, to determine if the conditioned response was associated with the specific drug condition of the organism during training. Virtually no dissociation was observed across different states. Animals trained at one dosage level and/or after an injection of physiological saline. Possible reasons for the lack of dissociation appeared to be the nature of the task and the minimal potential of methamphetamine to produce state dependent conditioning. 17 references. (Author abstract)

117010 Spencer, John; Holloway, Frank A. University of Oklahoma Health Sciences Center, 800 N.E.13, P.O.Box 26901, Oklahoma City, OK 73190 Differentiation between carbachol and eserine during deprivation-induced drinking in the rat. ***Psychonomic Science.*** **28(1):16-18, 1972.**

Differentiation between carbachol and eserine during deprivation induced drinking in the rat was studied. Direct application of carbachol to various diencephalic or limbic regions of the rat brain enhanced water intake over saline baseline at 0, 9, and 23 h deprivation, while at 47 h no differences were seen. Application of eserine produced an increase in water intake at only 0 h deprivation while norepinephrine had no effect at any level of deprivation. These results would suggest that endogenous cholinergic mechanisms may not mediate natural thirst in the rat. 11 references. (Author abstract)

117012 Grota, Lee J.; Ader, Robert. University of Rochester School of Medicine and Dentistry, Rochester, NY 14642 Effects of early experience with electric shock and dexamethasone on avoidance conditioning at adulthood. ***Psychonomic Science.*** **28(1):10-12, 1972.**

The effects of dexamethasone on adult avoidance behavior and plasma corticosterone levels was observed in rats subjected to electric shock stimulation and/or dexamethasone treatment during early life. In the absence of dexamethasone, early stimulation increased the number of avoidance responses. Dexamethasone did not influence avoidance behavior in any systematic manner, but did decrease corticosterone levels when administered at maturity. Electric shock stimulation during infancy resulted in lower corticosterone levels relative to unmanipulated controls whether or not these animals had been treated with dexamethasone. 16 references. (Author abstract)

117386 Belluzzi, James D. Dept.of Psychology, California State University, Chico, CA 95926 Long-lasting effects of cholinergic stimulation of the amygdaloid complex in the rat. ***Journal of Comparative & Physiological Psychology.*** **80(2):269-282, 1972.**

Injection of carbachol into the amygdaloid complex of rats caused EEG seizures and behavioral convulsions. After convulsions and abnormal EEG had disappeared, impaired acquisition of a one way active avoidance response and facilitated acquisition of a two way shuttle box avoidance response persisted. There was normal acquisition of an appetitive visual discrimination task, but not improvement in one way active avoidance acquisition following daily handling that facilitated acquisition in controls. Eserine injections into the amygdala produced a deficit in one way avoidance acquisition similar to that produced by carbachol, without altering EEG or inducing convulsions. It was suggested that the behavioral changes were due to altered amygdaloid synaptic function which elevated the animals' reactivity to noxious stimuli. 20 references. (Author abstract)

117592 Rabe, Ausma; Haddad, R.K. Bureau of Research in Neurology and Psychiatry, New Jersey Neuropsychiatric Institute, NJ 08540 Methylazoxymethanol-induced micrencephaly in rats: behavioral studies. ***Federation Proceedings.*** **31(5):1536-1539, 1972.**

The adaptive capacities of rats with severely reduced cerebral hemispheres from prenatal treatment with methylazoxymethanol acetate were tested on a number of different behavioral tasks. Various aspects of behavior were not uniformly affected. The micrencephalic rats were deficient on spatial reversal and maze type problem solving tasks, but were not impaired in their performance on commonly used operant conditioning schedules or in acquiring a discrimination learning set. The impairment of micrencephalic animals on a task of the problem solving type could be substantially reduced by favorable environmental conditions during rearing. The treated animals were found to be hyperactive. 17 references. (Author abstract)

117595 Angel, Charles; Bounds, Hugh M., Jr.; Perry, Alton. VA Center (520/151-1), Biloxi, MS 39531 A comparison of the effects of halothane on blood-brain barrier and memory consolidation. ***Diseases of the Nervous System.*** **33(2):87-93, 1972.**

The effects of exposure to halothane anesthesia at two different concentrations were evaluated as a variable affecting memory in mice subjects to a one trial passive avoidance learning procedure. A similar experimental design was utilized to test the effects of different concentrations of halothane on blood brain barrier in rats. A parallelism exists between the degree of disruption of brain barrier function and the trend toward amnesia production by different concentrations of halothane. 12 references. (Author abstract modified)

117609 Depoortere, H.; Loew, D.M. Dept.of Pharmacology, Biological and Medical Research Division, Sandoz Ltd., Basle, Switzerland Alterations in the sleep/wakefulness cycle in rats after administration of (L)-LSD or BOL-148: a comparison with (D)-LSD. ***British Journal of Pharmacology (London).*** **44(2):354P-355P, 1972.**

The effects of (D)-LSD on the sleep - wakefulness cycle of rats were compared with those of its levoratory isomer and its nonhallucinogenic bromine derivative BOL-148. Treatment with (L)-LSD at 1-3mg/kg did not change the content of the sleep - wakefulness cycle nor did it affect the quality of the phases. In particular, the drug did not cause any inhibition of the duration of paradoxical sleep. Treatment with BOL-148 led to a 27% decrease in paradoxical sleep and a 14% increase in slow wave sleep. Thus, (L)-LSD was found to be devoid of central activity whereas BOL-148 exerted definite central actions. Although less potent, BOL-148 has an activity which is similar to that of its hallucinogenic congener (D)-LSD. The two compounds differ in that (D)-LSD induces initial stimulation which is not seen following BOL-148 administration. The results are consistent with the view that the effects of (D)-LSD on the rat sleep electroencephalogram are not related to its hallucinogenic effects. 2 references.

117614 U'Prichard, D.C.; Steinberg, Hannah. Dept.of Pharmacology, Univ.College, London, England Selective effects of lithium on two forms of spontaneous activity. ***British Journal of Pharmacology (London).*** **44(2):349P-350P, 1972.**

The selective effects of lithium on spontaneous activity was investigated in the mouse. Mixtures of dexamphetamine combined with chlordiazepoxide markedly increased the activity of saline pretreated mice tested on the hole board. Activity after any dose of the separate drugs or a mixture containing 2.36mg/kg dexamphetamine and 25.0mg/kg chlordiazepoxide was not significantly different from controls injected with saline. Lithium pretreatment completely prevented the increase in activity produced by the mixtures but did not reduce the activity of animals in any of the other drug groups and slightly increased the activity of the saline control animals. In the photocell activity cages only one dose of dexamphetamine and the mixture containing this ingredient dose significantly increased activity. Lithium pretreatment, however, failed to prevent these increases. This may have been because the activity cages provided a qualitatively different environment with little scope for the characteristically manic hyperactivity observable on the holeboards, because the mice had already previously been tested, and because in any case photocells do not readily discriminate between various kinds of movement. 3 references.

117615 Beattie, I.A.; Berry, P.A.; Lister, R.E. Inveresk Research International, Musselburgh, Midlothian, Scotland Effect of oxypertine on anxiety-induced behaviour in baboons. ***British Journal of Pharmacology (London).*** **44(2):348P-349P, 1972.**

The effect of oxypertine on anxiety induced behavior was examined in baboons. Human intrusion was used to measure anxiety in the colony leader. Oxypertine produced a marked suppression of anxiety induced aggression in the leader of the colony. The effects of the drug were detectable 20 min after dosing and lasted for up to five hours. The maximal effects occurred 60-120 min after dosing. No sedation or other undesirable effects were recorded at these dose levels. Slight ataxia was seen after an oral dose of 8mg/kg oxypertine, though this effect was transient. No signs of sedation were detected at any dose level studied. 6 references.

117620 Everitt, B.J.; Hacket, N.B. Dept.of Pharmacology, Univ.of Melbourne, Parkville, Victoria, Australia Central stimulant action of fenfluramine in the rat. ***British Journal of Pharmacology (London).*** **44(2):342P-343P, 1972.**

The central stimulant action of fenfluramine was investigated in the rat. Three dose levels of DL-amphetamine and DL-fenfluramine, injected intraperitoneally, were used for calculation of the doses of each which produced a 200% increase in the average activity count over 25 min as compared to control rats tested at the same time. The following values were obtained: DL-amphetamine sulphate, 0.6mg/kg; DL-fenfluramine hydrochloride, 6.1mg/kg. These doses are anorectic in the rat and show that fenfluramine, like amphetamine, produces changes in the behavior of rats which are indicative of central nervous system stimulation. 4 references.

117635 Katz, D.M.; Steinberg, Hannah. Dept.of Pharmacology, Univ.College, London, England Previous environment and responses to morphine. ***British Journal of Pharmacology (London).*** **44(2):350P, 1972.**

The effect of previous environment on responses to morphine was examined in rats. In chronic experiments, previously grouped or isolated rats did not differ in the rates at which they learned to administer solutions of morphine. These results are discussed as to cause. The proportion of total fluid drunk in the form of morphine solutions when water was also available was taken as an index of dependence. Isolated and grouped rats made dependent on morphine by regular injections showed no differences in the amounts of weight lost after substitution of morphine by saline injections. The apparent absence of effects of previous isolation in the chronic experiments may be due to disturbances associated with the experimental procedures, especially as the first experiment had shown that the effects of isolation were labile since they could be abolished by short periods of grouping. It is unlikely that the modification of acute responses to morphine was simply due to general changes in the rate of metabolism of the drug, since the two responses that were measured showed opposite results. 4 references.

118074 Jones, B.E.; Prada, J.A. NIMH Addiction Research Center, Lexington, KY Relapse to morphine use in dog. Lexington, Ky., NIMH, 1972. 24 p.

The suitability of dogs for the study of relapse to morphine use was studied. Observations were made on 21 dogs under continuous reinforcement schedules. Responding during a 10 to 21 day control period was compared to that when morphine, at doses rangint from 0.01-0.25mg/kg per reinforcement, was substituted for saline for 14 to 21 days. Three dogs with amphetamine (0.05mg/kg per reinforcement) and three dogs offered treat food all learned to bar press for these rewards in one to four days. Six dogs were eventually trained to maintain dependence by self administration at levels of 10-20mg/kg/day. At intervals ranging from one to six months after abrupt withdrawal these dogs all resumed self administration of morphine and returned to the operant cage. Relapse to use of morphine typically occurred within minutes or hours of being replaced in the operant cage. It thus appears that in postaddict dogs that had self administered morphine during their addiction, effects other than those experienced during the initial exposure to morphine are responsible for relapse. 21 references. (Author abstract)

118751 Vogel, John R.; Leaf, Russell C. Squibb Institute for Medical Research, New Brunswick, NJ 08903 Initiation of mouse killing in non-killer rats by repeated pilocarpine treatment. ***Physiology & Behavior.*** **8(3):421-424, 1972.**

Some, but not all, laboratory rats spontaneously attack and kill mice. Repeated daily intraperitoneal administration of pilocarpine initiated mouse killing by all nonkiller rats. Thus, all rats possess brain mechanisms that control predatory attack and killing of mice. 18 references. (Author abstract)

118757 Holloway, Frank A. Department of Psychiatry and Behavioral Sciences, University of

Oklahoma, Oklahoma City, OK 73190 Effects of septal chemical injections on asymptotic avoidance performance in cats. *Physiology & Behavior.* 8(3):463-469, 1972.

The effects of application of neurohumors to the septal cholinergic neurons on the response inhibitory - excitatory parameter of behavior were studied. Double walled cannulae were implanted in the septal region of 16 cats. Injections of carbachol into dorsal midline septal placements significantly reduced the percentage of asymptotic, shuttlebox avoidance responses. Those animals demonstrating mild to moderate signs of overt behavioral change with carbachol were most impaired on the avoidance task. However, in contrast to the results for avoidance responses, the dorsal midline carbachol injections were found to significantly decrease the latencies of avoidance responses while norepinephrine increased avoidance response latencies. The production of overt behavioral effects and of shorter latency CARs (conditioned avoidance response) with the dorsal midline carbachol injections was discussed in terms of the possibility that cholinergic neurons in the dorsal midline septal area may mediate certain aspects of behavioral activation, possibly via their influence on the hippocampus. 26 references. (Author abstract)

118792 Florio, V.; Fuentes, J.A.; Ziegler, H.; Longo, V.G. Laboratori di Chimica Terapeutica, Istituto Superiore di Sanita, Rome EEG and behavioral effects in animals of some amphetamine derivatives with hallucinogenic properties. *Behavioral Biology.* 7(3):401-414, 1972.

A study on the central effects of four methoxy substituted amphetamines, of myristicin, and of macromerine has been carried out using 45 rats, 20 rabbits, and 4 cats bearing chronically implanted electrodes. In the rat and in the rabbit the amphetamine derivatives gave rise to a syndrome consisting of a mixture of depression and excitation. Activation of the EEG occurred after small doses of all the drugs, while high doses induced the appearance of spikes and, in some instances, of a grand mal seizure. In the rat, neurovegetative disturbances (vasodilatation) and ejaculation were observed with some of the compounds. Myristicin and macromerine influenced only slightly the EEG and the behavior. The cats, which were trained to an instrumental reward discrimination response, proved to be the most sensitive animal to the effect of these substances. The four amphetamine derivatives, in appropriate dosage, blocked conditioned behavior and caused bizarre behavioral (hallucinatory) patterns. The behavioral alterations were independent from the modifications of the EEG. A clear cut EEG activation has been observed only after DOM, while the other derivatives caused a mixed tracing, and with higher doses, synchronization. The correlation between the central activity of these compounds in the various animal species tested in these experiments and their hallucinogenic properties in man indicated that the conditioned cat is the best suited animal for research in this field, since a good relationship exists between the order of potency in disrupting the conditioned response and the human data. 21 references. (Author abstract)

118793 Araujo Carlini, Elisaldo Luiz; Lorenzo, Rubia Maria Tavares; Almeida, Edson Trijo. Departamento de Bioquimica e Farmacologia, Escola Paulista de Medicina, Rua Botucatu, Sao Paulo, Brazil A suggested aversive effect in rats of posttrial administration of central nervous system stimulants. *Behavioral Biology.* 7(3):391-400, 1972.

The effects of posttrial injections of amphetamine, pentylenetetrazol and strychnine on the performance of trained rats in a Lashley III maze and in a shuttle box were studied. The first two drugs, at doses of 2.0and 20.0mg/kg, respectively, were able to impair the performance of the animals after a few posttrial injections. Strychnine at doses from 0.2to 1.30mg/kg was ineffective. The disruption of performance produced by the two drugs was tentatively explained on the basis of an approach - avoidance conflict set up by some aversive properties of amphetamine and pentylenetetrazol. The mode of action of the three drugs was discussed to explain the lack of effect of strychnine. 29 references. (Author abstract)

118801 Meinecke, Richard O.; Cherkin, Arthur. Psychobiology Research Laboratory, Veterans Administration Hospital, Sepulveda, CA 91343 Failure of ethanol or pentobarbital to suppress fighting in the pit gamecock (Gallus gallus). *Psychopharmacologia (Berlin).* 25(2):189-194, 1972.

The pit gamecock (Gallus gallus) provides a model of strong trained aggression. A total of 16 aggressive pairs was treated with pentobarbital (40 or 60mg/kg, intramuscularly), or ethanol (10 to 30ml/kg of 33% v/v ethanol, by gastric intubation), or ethanol plus immobilization. Pairs of

treated cocks were allowed to recover together in one cage. Fighting behavior occurred immediately upon recovery of the second cock of each pair. Thus, recovery from anesthesia in pairs failed to attenuate aggressive behavior in the gamecock, contrary to the marked attenuation previously observed in the male rabbit. 6 references. (Author abstract)

118803 Guerrero-Figueroa, Roberto; Gallant, Donald M.; Galatas, Rivers F.; Rye, Merrill M. Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, LA 70112 Effects of yohimbine on CNS structures: Neurophysiological and behavioral correlations. *Psychopharmacologia (Berlin).* 25(2):133-145, 1972.

Yohimbine (by intravenous and/or intraperitoneal routes at doses between 0.5to 3mg/kg) produces behavioral changes (in moving cats and dogs) characterized by: a) an increase in alertness, extreme agitation, and nervousness; b) an increase in motor reaction to a variety of sensory stimuli; and c) an appearance of muscular shaking and tremors. These behavioral changes are associated with electrographic alterations characterized by: a) an increase in the amplitude of the local evoked potentials (LEP) recorded from the mesencephalic reticular formation, posterior hypothalamus and intralaminar thalamic system; b) a decrease in the amplitude of the LEP recorded from preoptic area, lateral hypothalamus and septal region; c) a slight diminution in the LEP amplitudes of the amygdala and hippocampus; d) an initial increase (15 to 25 min) followed by a long period of strong diminution in the amplitude of the cortical LEP; e) an increase in the percent time of fast cortical activity and in the amplitude of all frequencies; f) an appearance of subcortical and cortical epileptiform discharges in the normal animals during administration of the compound at doses of 2 to 3mg/kg; and g) a marked activation of epileptiform discharges in the subcortical or cortical epileptic animals in association with occasional clinical seizures. These results were discussed from the point of view of neuronal excitability changes in CNS structures. 24 references. (Author abstract)

118804 Bignami, Giorgio. Laboratori di Chimica Terapeutica, Istituto Superiore di Sanita, Viale Regina Elena 299, I-00161 Rome, Italy Facilitation of avoidance acquisition by LSD-25: possible effects on drive modulating systems. *Psychopharmacologia (Berlin).* 25(2):146-151, 1972.

LSD-25 (0.05 or 0.1mg/kg s.c.)facilitated the acquisition of discrete trial two-way avoidance by rats without causing marked changes in intertrial response frequency. Animals treated with 0.2mg/kg of the drug before each session showed little or no facilitation, while higher doses, which are known to exert a depressant action in the same and other avoidance situations, were not tested in this acquisition study. These results and other published data on avoidance, on other simple tasks and on go - no go discriminations indicate that LSD-25 may have a fairly selective effect on drive modulating systems, i.e.,cause a drive enhancement or disinhibition. The same data exclude gross changes in stimulus sensitivity as well as motor hyperactivity or a widespread impairment of response control (response disinhibition or perseveration). 26 references. (Author abstract)

118805 Hyyppa, M.; Lampinen, Pirkko; Lehtinen, Paivi. Department of Neurology, University of Turku, 20520 Turku 52, Finland Alteration in the sexual behaviour of male and female rats after neonatal administration of p-chlorophenylalanine. *Psychopharmacologia (Berlin).* 25(2):152-161, 1972.

p-Chlorophenylalanine (pCPA) was administered to male and female rats on the 2nd and 3rd (20 mg/kg) and on the 5th and 6th (100mg/kg) postnatal day. The display of spontaneous and hormone induced adult sexual behavior, the onset of puberty in the females, and the effect of the neonatal drug injections on serotonin and 5-hydroxyindole acetic acid levels in the brains of 15-day-old rats were examined. In the females, the time of vaginal opening was delayed even though the vaginal cytological cycles appeared to be normal. In addition, these females showed less ear wiggling activity during both spontaneous and hormone induced copulatory behavior and a tendency to shortening of mount latencies during hormone induced masculine sexual behavior. The drug treated males were, as adults, generally more sexually facile than were the vehicle treated controls: they required fewer mounts and intromissions prior to ejaculation, and displayed shorter intromission and ejaculation latencies as well as shorter refractory periods and intervals between successive intromissions. The hormone induced female sexual behavior in the drug treated males appeared, however, to be unaltered. Finally, although many differences in adult sexual behavior were observed in the animals treated with pCPA shortly after birth, no changes or sex

differences in hypothalamic or forebrain concentrations of serotonin or 5-hydroxyindole acetic acid were found in animals treated similarly in infancy but killed at the age of 15 days. The relevance of these findings is discussed in the light of the possible significance of brain indole amines during the sexual development and differentiation. 25 references. (Author abstract)

05 TOXICOLOGY AND SIDE EFFECTS

112168 Harbison, Raymond D.; Mantilla-Plata, Bernardo. Department of Pharmacology, Vanderbilt Medical Center, Nashville, Tenn. 37203 Prenatal toxicity, maternal distribution and placental transfer of tetrahydrocannabinol. ***Journal of Pharmacology and Experimental Therapeutics.*** **180(2):446-453, 1972.**

Tetrahydrocannabinol (delta9-THC) was embryocidal or fetocidal when administered to pregnant mice. Delta 9-THC administered on days 8 and 9 of gestation produced about 70% incidence of in utero deaths. Delta9-THC induced about 30% incidence of in utero deaths when administered on gestational days 10 and 11 or days 12 and 13. Delta9-THC also significantly reduced fetal body weight. Again, there was a gestational period susceptibility. After i.p. administration of C-labeled delta9-THC, C was measured in maternal plasma. The greater accumulation of C was found in maternal fat and liver tissue. Smaller amounts of C were measured in maternal kidney, muscle and brain tissue. Delta9-THC was transferred across the placenta and was measured in fetal tissue and amnionic fluid. Excretion of the drug was primarily by feces and at 120 hours after injection about 10% of the dose remained in the animals. Maximum excretion of delta9THC in the urine was about 10%of the administered dose. Thus, delta9-THC is transfereed across the placenta and is embryocidal or fetocidal. 25 references. (Author abstract)

113165 Gralla, E.J.; McIlhenny, H.M. Yale Univ.School of Medicine, 220 S.Frontage Rd., New Haven, CT 06510 Studies in pregnant rats, rabbits and monkeys with lithium carbonate. ***Toxicology and Applied Pharmacology.*** **21(3):428-433, 1972.**

Lithium carbonate was examined for absorption and effects on fetal development, reproduction, gestation and lactation in rats. Companion studies were completed in rabbits and rhesus monkeys in which pregnant females received lithium carbonate during organogenesis. A low incidence of maternal mortality occurred at the highest dose levels administered to rats (4.05 meq/kg/day) and rabbits (1.08 meq/kg/day). Body weight gain of neonatal rats was somewhat inhibited when nursing females were given 4.05 meq/kg/day. No drug related congenital abnormalities were detected in either rats, rabbits or monkeys. Lithium carbonate appears to have no serious effect on reproduction in these 3 species at maximum subtoxic levels. 28 references. (Author abstract modified)

113166 Torchiana, Mary Lou; Wenger, Herbert C.; Lagerquist, Barbara; Morgan, George M.; Stone, Clement A. Merck Institute for Therapeutic Research, West Point, PA 19486 Pharmacological antagonism of the toxic manifestations of amitriptyline and protriptyline in dogs. ***Toxicology and Applied Pharmacology.*** **21(3):383-389, 1972.**

In unanesthetized dogs intoxication with amitriptyline produced tachycardia and neurologic changes characterized chiefly by agitation and restlessness. The chronotropic actions of such intoxication were reduced by inhibitors of cholinesterase (physostigmine, pyridostigmine), by mecamylamine, a ganglionic blocking agent, and by propranolol, a beta-receptor blocking agent. Neurologic patterns were favorably influenced only by physostigmine. Protriptyline, given in toxic doses, produced a lesser degree of tachycardia, did not cause neurologic disturbances and was less susceptible to physostigmine reduction of heart rate changes than amitriptyline. The data suggest that the weak anticholinergic activities of amitriptyline and protriptyline may be responsible for some of the toxic manifestations. Activation of the sympathetic nervous systems may participate to some extent in the tachycardia. 11 references. (Author abstract)

114071 Meltzer, H.Y. Dept.of Psychiatry, Univ.of Chicago, 950 E.59th St., Chicago, Ill. 60637 Muscle toxicity produced by phencyclidine and restraint stress. ***Research Communications in Chemical Pathology and Pharmacology.*** **3(2):369-382, 1972.**

Muscle toxicity produced by phencyclidine and restraint stress was examined in the rat. The increase in plasma creatine phosphokinase (PCPK) levels in 150 gram male Sprague-Dawley rats produced by restraint at room temperature (RRT) for 30 min was significantly enhanced by pretreatment with phencyclidine (Phen), a potent

psychotomimetic agent in man, in doses from 0.5-10mg/kg, i.p.but not by doses of 15-50mg/kg, i.p. Large amounts of Type III (skeletal muscle) CPK and smaller amounts of Type I (brain type) CPK were present in rat plasma following Phen and RRT. The increases in PCPK levels produced by restraining guinea pigs or by other forms of stress in the rat were not affected by pretreatment with Phen. Phen, 5mg/kg, i.p.prior to 2 hours RRT produced skeletal muscle injury observable in frozen sections and in Araldite-embedded muscle. The toxic effects of Phen and restraint stress on rat skeletal muscle may be of particular interest as a possible animal model for the recently discovered muscle abnormalities found in some acutely psychotic patients. 18 references. (Author abstract modified)

114785 Saunders, Donald R.; Miya, Tom S.; Mennear, John H. School of Pharmacy and Pharmacal Science, Purdue Univ., Lafayette, IN 47907 Chlorpromazine-ultraviolet interaction on mouse ear. ***Toxicology and Applied Pharmacology.*** **21(2):260-264, 1972.**

Two methods of assessing hyperpigmentation and phototoxic liability in mice were studied with chlorpromazine (CPZ) and ultraviolet (UV) light used as the test stimuli. Photoresistance and water content of the ear were found to be increased in both albino and C57B1 mice receiving both CPZ and UV. Label incorporation from 3,4-dihydroxyphenylalanine-2-14C into the ear was increased in the C57B1 mice, but not in the albino mice. It is suggested that measurement of photoresistance would be useful in assessing phototoxic and/or inflammatory liability while label incorporation would be useful in assessing hyperpigmentation liability. 7 references. (Author abstract)

114786 Beall, James R. Research Division, Schering Corp., Bloomfield, NJ 07003 A teratogenic study of chlorpromazine, orphenadrine, perphenazine, and LSD-25 in rats. ***Toxicology and Applied Pharmacology.*** **21(2):230-236, 1972.**

A teratogenic study of chlorpromazine, orphenadrine, perphenazine and LSD-25 to determine the effects of the compounds upon rat offspring was made. Pregnant rats were treated with either perphenazine, chlorpromazine, orphenadrine or LSD-25 on days 6 through 15 after mating. On day 21, the pups were removed and examined for gross, visceral and skeletal defects. The dams were examined for nidations, resorptions and reproductive performance. In all, 265 dams and 3454 offspring were evaluated. The results indicate that pregnant rats treated with near lethal doses of perphenazine or chlorpromazine have more resorptions than controls. At one or more doses of all drugs, average offspring weights were less than control values. Visceral examination of the pups revealed that seven dams from the two highest orphenadrine groups had abnormal offspring. In these groups, eight of 157 pups had enlarged, darkened bladders. One abnormally developed pup was produced in the low dose chlorpromazine group. All other rats treated with perphenazine, chlorpromazine or LSD-25 had normally developed offspring. 24 references. (Author abstract modified)

116090 Shuval, Hillel I.; Gruener, Nachman. Environmental Health Laboratory, Hebrew Univ.-Hadassah Medical School, Jerusalem, Israel Epidemiological and toxicological aspects of nitrates and nitrites in the environment. ***American Journal of Public Health.*** **62(8):1045-1052, 1972.**

Part of a broad spectrum program to reevaluate current nitrate and nitrite standards for water and food is reported. Field studies among infants in areas with varying concentrations of nitrates in water supplies as well as experimental studies on laboratory animals are included. Findings are reported and discussed. The detection of irreversible electrical brain activity changes in rats receiving low doses of nitrites in drinking water is of particular concern. 19 references. (Author abstract modified)

117585 Hirono, Iwao. Department of Pathology, Gifu University School of Medicine, Gifu-City, Japan Carcinogenicity and neurotoxicity of cycasin with special reference to species differences. ***Federation Proceedings.*** **31(5):1493-1497, 1972.**

The incidence of neurotoxicity and localization of tumors in rats and mice that received a single administration of cycasin were compared with similar groups of different species of animals (hamsters, rabbits and guinea pigs). In hamsters, hepato - cellular carcinomas were induced with cycasin only in newborns. A high incidence of proliferative changes and carcinomas of the intrahepatic bile ducts, rare in either rats or mice, was observed in newborn and adult hamsters. Kidney tumors were very rarely observed in hamsters. Young adult rabbits and guinea pigs

received a single oral administration of cycasin in dosage near LD50 level, however, neither animals developed tumors. Cycasin failed to induce clinical signs of neurologic disorders in rats as it had in mice and hamsters. The cerebellar lesions in rats were not as severe as those in mice and hamsters. The retinal lesions induced by a single administration of cycasin were much more severe in rats than in mice. 10 references. (Author abstract modified)

117587 Mettler, Fred A. College of Physicians and Surgeons, Columbia University, New York, NY 10032 Neuropathological effects of sodium ozide administration in primates. ***Federation Proceedings.*** **31(5):1504-1507, 1972.**

A review of the circumstances governing the experimental use of sodium azide a known neurotoxic agent capable of damaging portions of the brain, such as the substantia nigra, which are commonly involved in parkinsonism in primates is presented. It has thus far not been possible to reproduce such lesions with cycad derivatives which have been suspected as being responsible for the parkinsonism -dementia (P-D) complex. Very different experimental neuropathological findings have been obtained depending on the animal species employed, the size, method and length of time of dosage, and the occurrence or nonexistence of free periods in the dosage schedule. If cycasin is a responsible etiologic factor in the P-D complex, it is probable that any experimental situation employing it may profit by avoidance of such factors as may limit the utility of azide. 16 references. (Author abstract modified)

117588 Jones, Margaret; Yang, Modesto; Mickelsen, Olaf. Department of Pathology, Michigan State University, East Lansing, MI 48823 Effects of methylazoxymethanol glucoside and methylazoxymethanol acetate on the cerebellum of the postnatal Swiss albino mouse. ***Federation Proceedings.*** **31(5):1508-1511, 1972.**

The sequence of pathological changes induced by postnatal injection of methylazoxymethanol (MAM) acetate or methylazoxymethanol glucoside (cycasin) in the cerebellum of the Swiss albino mouse was determined. Gross changes in the cerebellum, including reduction in mass and complexity of folia, were obvious at five days. Cellular necrosis was maximal at two days and most necrotic elements were removed by three days posttreatment. The amount of cellular necrosis was more variable following cycasin administration and cell proliferation continued in the incompletely destroyed external differentiating cell layers. Diminution or complete depletion of granule cells was noted at later posttreatment intervals. The destructive effects of both compounds on differentiating cells in the postnatal brain were most marked in the cerebellum. The disturbed cerebellar cytoarchitecture induced by MAM acetate or cycasin resembled the granuloprival cerebellar hypoplasia caused by a wide variety of chemical, physical, and infectious agents. 11 references. (Author abstract modified)

117589 Jones, Margaret; Sweeley, Charles; Yang, Modesto. Department of Pathology, Michigan State University, East Lansing, MI 48823 Lipid composition of the cerebellum and spinal cord in postnatal cycasin-treated Swiss albino mice: preliminary observations. ***Federation Proceedings.*** **31(5):1512-1515, 1972.**

Lipid composition of the cerebellum and spinal cord in postnatal cycasin treated Swiss albino mice was investigated. Clinical abnormalities were noted at several postinjection intervals. Males from treatment and control litters were sacrificed at 25-days-old. The spinal cord and cerebellum were removed and lipid extracts were prepared from individual samples. Total phospholipids and cholesterol and individual lipid rations were determined. The reduced weight of the pathological cerebellum in treated animals was accompanied by a concomitant reduction in total phospholipids and cholesterol. At higher doses of cycasin, phospholipids were depressed in the histologically normal spinal cord of treated animals. The disturbed ration of individual phospholipids in this treatment group was primarily related to depression of the phosphatidylethanolamine fraction. 16 references. (Author abstract)

117590 Hirano, Asao; Jones, Margaret. Albert Einstein College of Medicine, Bronx, NY 10467 Fine structure of cycasin-induced cerebellar alterations. ***Federation Proceedings.*** **31(5):1517-1519, 1972.**

The fine structure of cycasin induced cerebellar alterations were examined. Cycasin was administered to mice within 24 hours after birth. Those animals which developed severe ataxia were sacrificed at 25 days of age and the cerebellar cortex was examined with the electron

microscope. The number of granule cells and their processes including the presynaptic terminals were greatly reduced. In spite of the absence of presynaptic terminals, dendritic spines arising from the Purkinje cells were present and maintained their principal morphological features including the postsynaptic membranous thickening. 6 references. (Author abstract)

117591 Haddad, R.K.; Rabe, Ausma; Dumas, Ruth. Bureau of Research in Neurology and Psychiatry, New Jersey Neuropsychiatric Institute, Princeton, NJ 08540 Comparison of effects of methylazoxymethanol acetate on brain development in different species. ***Federation Proceedings.*** **31(5):1520-1523, 1972.**

The effects of methylazoxymethanol acetate on brain development were examined in different species. The cerebral mass of the rat, hamster, and ferret was reduced by prenatal treatment with methylazoxymethanol acetate, while the structure of the cerebellum of the rat, hamster, rabbit, ferret, cat, and dog, but not of the pig, was readily modified by treatment of the newborn animal. The functional consequences varied considerably in different species. Severe and permanent motor dysfunction was observed in hamsters and ferrets; in cats and rats the functional consequences were milder and, in part, transitory. Some rabbits developed an incapacitating neuromuscular condition, while others with what appeared to be an equally deranged cerebellum showed only transitory motor symptoms. In the monkey, only subtle deficits in sensory - motor performance were seen, while the pig showed no functional deficit. 16 references. (Author abstract modified)

117593 Sanger, V.L.; Yang, M.; Mickelsen, O. Department of Pathology, Michigan State University, East Lansing, MI 48823 Cycasin-induced central nervous system lesions in postnatal mice. ***Federation Proceedings.*** **31(5):1524-1528, 1972.**

Cerebellar hypoplasia in mice and puppies induced by injection of cycasin and methylazoxymethanol acetate is reported. At 25 days of age, experimental mice exhibited neurological disturbances characterized by tremors, swaying of rear quarters, goose stepping, and falling. At this time both experimental and control mice were killed and their brains and spinal cords were removed and examined histologically. Cerebellar lesions were found that were characterized by disorganization and reduced cell numbers in the granular layers. Purkinje cells were disorganized. In another study, newborn mongrel puppies were injected subcutaneously with varying doses of methylazoxymethanol acetate. Levels higher than 0.05microliter/g of body weight caused death in about seven days. When 0.025microliter/g of body weight was injected the dogs lived longer than 35 days. By one week of age, experimental puppies were lighter in weight, weaker than the control pups; and had rough hair coats. At 30 days, hindquarter paralysis was suspected but toe pinch reflex and pain could be elicited. 14 references. (Author abstract modified)

117594 Malevski, Y.; Yang, M.G.; Sculthorpe, A.; Sanger, V.L.; Mickelsen, O. Department of Food Science and Human Nutrition, Michigan State University, East Lansing, MI 48823 Hypothalamic and pituitary hormonal changes in rats injected with methylazoxymethanol acetate. ***Federation Proceedings.*** **31(5):1530-1535, 1972.**

The effects of methylazoxymethanol (MAM) acetate on the length of the estrous cycle and on the levels of luteinizing hormone (LH) and prolactin in the blood and pituitary and on their releasing and inhibing factors in the hypothalamus were studied in the rat. In those rats injected with MAM acetate, estrous cycles were significantly prolonged, mainly by an increased length of the diestrus stage. For approximately eight days after the injections, the ovaries were filled primarily with corpora lutea. The uteri at this time were significantly lighter and contained only a few glands, had a narrow lumen and a dense endometrium. Blood prolactin concentrations were unchanged whereas blood concentrations were decreased. Prolactin and LH in the pituitary were decreased but only for three days after the injection. The quantity returned to normal subsequently. Pair fed control and positive control rats had normal estrous cycles, normal ovaries and uteri. They also had normal levels of blood and pituitary prolactin and LH. 16 references. (Author abstract modified)

117611 Alhava, Eeva; Mattila, M.J. Dept.of Pharmacology, Univ.of Helsinki, SF-00170 Helsinki 17, Finland Amphetamine toxicity and brain amphetamine concentration in adult and developing mice. ***British Journal of Pharmacology (London).*** **44(2):352P-353P, 1972.**

Amphetamine toxicity and brain amphetamine concentrations in adult and developing mice were investigated. Doses of DL-amphetamine sulphate

were given to adult mice, 3-5-day-old mice and to 32-35nday-old mice. The highest concentrations of amphetamine were reached within 15 min after injection in the adult brain and heart. The concentrations then steadily declined. In mice 32-35-days-old the peak amphetamine concentration in brain was higher and was reached within 30 min, and its decline was rapid. In contrast, in mice 3-5-days-old the brain amphetamine concentration was lower than that measured in adult mice at 30 min and continued to rise with time. In this age group, the heart amphetamine concentration was slightly higher than brain amphetamine 15 and 30 min after injection, and did not change significantly up to 120 minutes. The low concentrations of brain amphetamine in the youngest age group and the delay in reaching the peak may well contribute to the relative resistance of these animals to amphetamine. 4 references.

118354 Christian, Samuel T.; Janetzko, R. NIMH, Addiction Research Center, Lexington, KY The interaction of phenothiazine derivatives with synaptosomal membranes: the use of fluorescent probes as an indicator of drug-induced conformational perturbations. (Unpublished paper). Lexington, KY, NIMH, 1972. 25 p.

The effects of two phenothiazine derivatives, chlorpromazine and chlorpromazine sulfoxide, were studied on postsynaptic membranes derived from rat cerebral cortex. The fluorescent probe 1-anilino-8-naphthalene sulfonate (ANS) was used to determine whether these drugs were capable of actually altering membrane structure. The results indicate that ANS is bound to the membrane resulting in an enhanced fluorescence and a blue spectral shift of some 43nm in its emission spectrum. Titration of the ANS-membrane complex in the presence of chlorpromazine indicated that the drug alters the membrane structure in such a way as to create additional ANS binding sites. This finding was verified by the use of double reciprocal plots of protein versus fluorescence in the presence and absence of the drug. When chlorpromazine sulfoxide was used as the neuroperturbant the same effect was noted but to a much smaller degree. These findings substantiate theories regarding the mechanism of action of these drugs and show that not only do psychoactive agents have the ability to alter neuronal membrane structure but that the fluorescent probe technique may prove to be useful in studying such events in isolated in vitro preparations at the molecular level. 39 references. (Author abstract modified)

118795 Rosenblatt, Jack E.; Janowsky, David S.; Davis, John M.; El-Yousef, M.Khaled. Depts.of Psychiatry and Pharmacology, Vanderbilt Univ.School of Medicine, Tennessee Neuropsychiatric Inst., Nashville, TN 37217 The augmentation of physostigmine toxicity in the rat by delta9-tetrahydrocannabinol. *Research Communications in Chemical Pathology and Pharmacology.* 3(3):479-482, 1972.

Sprague-Dawley rats were treated with delta9-tetrahydrocannabinol (delta9-THC) (2mg/kg) and physostigmine salicylate (0.4mg/kg) or with physostigmine salicylate alone. Seventeen rats received the combined THC - physostigmine treatment; of these animals, 13 died and 4 survived. Seventeen rats received physostigmine salicylate and propylene glycol serum complex without THC; of these animals, 2 died and 15 survived. This difference was highly significant (p less than .0002). Both atropine and methylscopolamine decreased the lethality of the THC - physostigmine combination. Delta9-THC appears to augment physostigmine toxicity in the rat. 5 references. (Author abstract)

118796 Sokol, G.H.; Maickel, R.P. Department of Pharmacology, Medical Sciences Program, Indiana University, Bloomington, IN 47401 Toxic interactions of d-amphetamine and tricyclic antidepressants in mice. *Research Communications in Chemical Pathology and Pharmacology.* 3(3):513-521, 1972.

The interaction of various tricyclic drugs with d-amphetamine toxicity has been studied under standard conditions in nonaggregated mice. Pre- or posttreatment with promazine protects the animals in all cases. The tertiary amines, imipramine and amitriptyline, have either no effect or exert a protective action, while the secondary amines, desmethylimipramine and nortriptyline, either potentiate or reduce the toxicity of d-amphetamine, depending on the dosage schedule with respect to time. Imipramine has no significant effect when administered after the amphetamine, but it has a protective effect when administered 4 hours prior to the amphetamine. Desmethylimipramine also has a protective effect when administered 4 hours prior to the amphetamine, although it acts as a potentiator of toxicity when given 30 min or less prior to the

amphetamine. Neither amitriptyline nor nortriptyline give significant protection when given after the amphetamine; however, amitriptyline affords protection when given 15 min prior to the amphetamine, while nortriptyline potentiate the lethal effects of the amphetamine when administered on the same time schedule. Promazine has a protective effect whether given before or after the amphetamine. 12 references. (Author abstract modified)

118807 Phillips, Richard N.; Brown, Daniel J.; Martz, Robert; Hubbard, J.Donald; Forney, Robert B. Department of Toxicology, Indiana University School of Medicine, Indianapolis, IN 46202 Subacute toxicity of aqueous-suspended delta9-tetrahydrocannabinol in rats. ***Toxicology and Applied Pharmacology.*** **22(1):45-49, 1972.**

An aqueous suspension of THC was prepared for subacute toxicity studies as follows: Thailand marihuana plant stock was extracted; the purity of the delta9-tetrahydrocannabinol (THC) obtained was 99% as determined by nuclear magnetic resonance, mass spectroscopy, and gas - liquid chromatography. The purity of the THC in water remained at 99%. Fifty male albino Holtzman rats were given daily ip injections (3.75 to 30mg/kg) of aqueous suspended THC for 30 days. Animals receiving the highest doses of THC exhibited the following signs approximately 10 min after the injection: hypersensitivity to auditory or tactile stimulation, depression, ataxia, lacrimation, and diarrhea. Animals receiving lower doses of THC exhibited the same signs but to a lesser degree. At the end of the 30 day test period, the body weight of the highest dose group was significantly less than that of the control group. Increases in the number of large hyperchromatic hepatic cells, some of which were binucleated, were found in some livers at three of four dose levels. It was also noted that the rats appeared to become more sensitive to THC during the last 10 days of the 30 day test period. 13 references. (Author abstract modified)

06 METHODS DEVELOPMENT

106973 Wursch, M.S.; Otis, L.S.; Green, D.E.; Forrest, I.S. Department of Psychiatry, Stanford University School of Medicine, Palo Alto, California 3H-delta-9-tetrahydrocannabinol (THC) metabolism in rhesus and squirrel monkeys. (Unpublished paper). Rockville, Md.NIMH, 1972, 7 p.

Male rhesus and squirrel monkeys were used in an attempt to find a suitable primate model for in vivo metabolism of delta-9-tetrahydrocannabinol (delta-9-THC). The data for gross total urinary and fecal elimination of labeled delta-9-THC after oral ingestion by the squirrel monkeys clearly indicated that this species is not a suitable primate model. However, the corresponding data for the rhesus monkeys were quite similar to those obtained in experiments with man. Very little information is available at this time on in vivo metabolism of the cannabinoids and delta-9-THC in particular. 8 references.

107601 Spano, P.F.; Costa, E. Preclinical Pharmacology Lab., NIMH, St.Elizabeths Hospital, Washington, D.C. 20032 Ring substituted indolealkylamines present in rat hypothalamus. (Unpublished paper). Washington, D.C.NIMH, 1972.

Ion exchange chromatography was used to separate 6-hydroxytryptamine (6OT) added to brain homogenates and a fluophore was obtained which was specific for 6-hydroxy indole ethyl amine. The fluophore is also formed by 6-hydroxytryptophan and requires that the 5 position in the indole ring is free. 6OT could not be detected in the hypothalamus of rats. About 0.6nanomole/g of this amine was found in the brain stem of rats receiving pargyline (75mg/kg) followed by 10mg/kg i.v.of Dl-6-hydroxytryptophan. By reacting with ninhydrin extracts of hypothalamus purified with butanol extraction, the formation of the fluophore was detected which, on the basis of longer time required for its formation, would be differentiated from 5-hydroxytryptamine (5-HT). This delayed reaction was obtained with N-acetyl 5-HT, N-methylserotonin, and melatonin added to brain extract. (Author abstract modified)

108965 Choulis, Nicolas H. School of Pharmacy, West Virginia University, Morgantown, W.Virginia 26506 Conductimetric studies of interactions of optically active ions I: interactions of amphetamine with mandelic and tartaric acids. ***Journal of Pharmaceutical Sciences.*** **61(2):293-294, 1972.**

The conductances of 0.006M aqueous solutions of d-amphetamine and l-amphetamine were measured in equimolar aqueous solutions of d-mandelic acid, l-mandelic acid, d-tartaric acid, and l-tartaric acid. Conductivity changes were recorded, and the results were interpreted in terms of ionic associations. 6 references. (Author abstract modified)

111791 Dhahir, H.I.; Jain, Naresh C.; Thornton, John I. Indiana University Medical Center, Indianapolis, Indiana 46207 The identification of ibogaine in biological material. ***Journal of the Forensic Science Society (London).*** **12(1):309-313, 1972.**

A reliable method is described for the extraction of unchanged ibogaine from biological materials such as blood, urine, and tissue homogenates of liver, kidney, and brain by a simple extraction for basic drugs. An indole alkaloid extracted from the root of a West African plant ibogaine has a purported hallucenogenic affect and its prescription and use are controlled by the Federal Drug Abuse Contro Act. Precise identification of the alkaloid may be achieved through the use of thin-layer chromatography, ultraviolet and infrared spectrophotometry. 16 references. (Author abstract)

113115 Moreton, J.E.; Davis, W.M. School of Pharmacy, University of Mississippi, University, MS 38677 A simple method for the preparation of injectables of tetrahydrocannabinols and cannabis extracts. ***Journal of Pharmacy and Pharmacology (London).*** **24(2):176, 1972.**

A simple, inexpensive method of producing a reliable aqueous suspension of tetrahydrocannabinols and cannabis extracts is reported. Frozen 1-trans-delta9-tetrahydrocannabinol or 1-trans-delta8-tetrahydrocannabinol or marihuana extract distillate was mixed in a glass mortar and pestle with a quantity of Arlacel-20 equal to 2% (w/v) of the intended final volume until all material was dissolved. An equal amount of Tween-65 was then added and thoroughly mixed. One ml of physiological saline was added and mixed to form a creamy suspension. This was repeated several times and then the suspension made up to produce suspensions containing 20mg/ml of the drug. The drugs were rapidly released from the suspension as indicated by behavioral and EEG measurements, while the control vehicle was found to be inactive. 1 reference.

CLINICAL PSYCHOPHARMACOLOGY

07 EARLY CLINICAL DRUG TRIALS

107691 Tischler, Bluma; Patriasz, Klara; Beresford, Jane; Bunting, Rosamund. Woodlands School, New Westminster, B.C., Canada Experience with pericyazine in profoundly and severely retarded children. ***Canadian Medical Association Journal (Toronto).*** **106(3):136-141, 1972.**

The effectiveness of pericyazine in severe behavioral disorders was evaluated in 15 profoundly and severely retarded children. Pericyazine provided significant improvement in such parameters as cooperation, temper, purposeless activities, hyperactivity, communication and mood. It proved to be statistically superior to the minor tranquilizers in improving cooperation and helpfulness, temper, mood, the understanding of commands and table manners, and in reducing self-abusiveness and abusiveness to staff. The safety of this agent was confirmed and photosensitivity was not found to be associated with its use. 10 references. (Author abstract)

111339 Brown, G.La Vonne; Green, Robert L., Jr.; Martin, Robert M., Jr. Duke University Medical Center, Durham, N.C. Double-blind, noncrossover study of imipramine and A-10749. ***Journal of Clinical Pharmacology and New Drugs.*** **12(1):40-45, 1972.**

1, 2-diisopropylurazole (A-10749) prepared as the sodium salt, was studied as an antidepressant and appeared to evince antidepressant activity comparable to imipramine in human subjects. Because of its antidepressant activity (somewhat less than imipramine in this study) and its low order of side effects, it is felt that A-10749 should be investigated further for its clinical usefulness. It is suggested that further studies would prove its effectiveness, especially studies of its effect on tryptophan metabolism. 25 references. (Author abstract modified)

111342 Weissman, Lester; Moore, James D.; Thomas, Gordon B.; Whitman, Erwin N. Department of Medical Pharmacology, Hoffmann-LaRoche, Nutley, New Jersey Personality factors in prison volunteers related to response in clinical drug trials. ***Journal of Clinical Pharmacology and New Drugs.*** **12(1):5-10, 1972.**

Environmental and personality factors exist which make a prison volunteer group distinct from the general public. In order to identify the differences and then attempt to determine whether these differences affected reaction to trial medication, the Minnesota Multiphasic Personality Inventory (MMPI) was used. The personality profile of the prisoner volunteers at Montana State Prison was identified and compared with reported profiles from other prison groups and from other population groups. Abnormal scores occurred predominantly in the psychosociopathic, hypomanic, and schizoid behavior scales. Several observers have reported that individuals with high scores in the above scales tend to underreact in drug trials; that is they suppress drug effects consciously or unconsciously. Based on a specific experiment designed to test response to drugs, the volunteer group at Montana State Prison did not tend to underreact and the data derived from this group, particularly in the area of drug tolerance, appeared to be reliable in well designed, carefully conducted trials. Personality and behavior patterns have important influences on clinical investigation. Careful consideration of these factors must be made particularly when study samples differ from the general population. 8 references. (Author abstract modified)

113377 Carney, M.W.P.; Sebastian, J.; Savarirayan, S.; Watts-Tobin, Carney, M.W.P.; Sebastian, J.; Savarirayan, S.; Watts-Tobin, M.A. 382 Clifton Drive North, St.Annes-on-Sea, Lancashire, United Kingdom Pilot trial of Ciba 34276-Ba. ***Psychopharmacologia (Berlin).*** **23(1):96-98, 1972.**

Results of a pilot trial of Ciba 34276-Ba suggest that it has antidepressant action in neurotic and psychotic depression. Because it was apparently effective in patients with marked psychomotor changes, the drug may well be a substitute for electroconvulsive treatment in certain patients for whom there is presently no effective alternative. Mode of action was rapid. Side effects, though numerous, were generally trivial. 3 references.

113971 Hanson, Rebecca A.; Menkes, John H. Department of Neurology, Kaiser Permanente Foundation, 4900 Sunset Boulevard, Los Angeles, California 90027 A new anticonvulsant in the management of minor motor seizures. ***Developmen-***

***tal Medicine and Child Neurology.* 14(1):3–14, 1972.**

Clonazepam, a new benzodiazepine, has been used to treat intractable minor motor seizures in 59 patients in the pediatric to young adult age range over a period of 18 months. The drug was effective in controlling seizures completely, adequately, or by at least 50% , in 76% of the 59 patients for at least 3 months, and in 65% for periods up to 18 months. The most dramatic and long term results occurred in patients with absence attacks, myoclonic jerks, and 'salaam' seizures. The experience in treating infantile spasms with clonazepam has, thus far, been disappointing. The major advantages of clonazepam are a low incidence of size effects, a rapid onset of clinical action after oral administration, and sufficient anticonvulsant efficacy to allow withdrawal of other drugs. 24 references. (Author abstract)

115197 Phillips, Eileen M.; Woolnough, Michael; Marinova, Vera M.; Turner, Paul. Dept.of Clinical Pharmacology, St.Bartholomew's Hospital, London, E.C.1, England A comparison of isoprenaline, salbutamol, and rimiterol inhalation on skin temperature, heart rate, and respiration in man. *Journal of Clinical Pharmacology and New Drugs.* 12(4):158-168, 1972.

Cardiorespiratory, bronchial, and skin vessel responses to inhalation of isoprenaline, salbutamol, rimiterol (WG 253), and placebo were investigated in double-blind trials in normal volunteers. Isoprenaline induced changes in all measurements, confirming universal beta-adrenoceptor agonism. Salbutamol in low dose induced selective beta2-bronchial receptor effects, and in high dose had action similar to isoprenaline. Rimiterol had selective beta2-adrenoceptor effects on bronchus alone under the conditions of the experiment. No evidence was gained that adrenergic vasodilator responses in the skin are mediated by selective beta2-agonists. The problems of pharmaceutical and biological availability of drugs prepared in identical formulations for the purpose of double-blind clinical trials are discussed. 8 references. (Author abstract)

117612 Bond, A.J.; Lader, M.H. Dept.of Psychiatry, Institute of Psychiatry, Univ.of London, London, England Residual effects of a new benzodiazepine: flurazepam. *British Journal of Pharmacology (London).* 44(2):343P-344P, 1972.

Residual effects of a new benzodiazepine, flurazepam were studied in eight normal human subjects. Ss received four treatments at weekly intervals and were given physiological tests, and psychological tests. The physiological tests consisted of EEG recordings during an auditory reaction time task and the average evoked response (AER) to the same task. All wave bands showed significant changes which persisted through the day up to 18 h after the drug; for example, the 4.0-7.5Hz wave band was significantly decreased by both drugs. A particularly sensitive measure was the mean voltage of the wave bands calculated as a percentage of the total voltage. Two components of the AER were significantly diminished. However, reaction time was not affected. These results confirm the persistent physiological changes which occur after single doses of hypnotics and emphasize the need for caution in evaluating studies of psychiatric patients receiving night sedation compared to normal controls not taking sleeping tablets. 2 references.

08 DRUG TRIALS IN SCHIZOPHRENIA

108808 Gallant, D.M.; Bishop, M.P. Tulane University School of Medicine, New Orleans, La. Quide vs. mellaril in chronic schizophrenic patients. Quide vs. mellaril in chronic schizophrenic patients. *Current Therapeutic Research.* 14(1):10-16, 1972.

Piperacetazine and thioridazine gave similar results in a study of therapeutic efficacy in 20 chronic schizophrenics. A treatment period of at least 10-12 weeks is recommended for testing antipsychotic drug efficacy. An increased dosage of piperacetazine (more than the usual dose) seemed to give better clinical improvement, but increased transaminase levels with this dosage suggest the need for liver monitoring during a heavy dosage regimen. 5 references.

108809 Menon, M.Sarada; Ramachandran, V. Government Mental Hospital, Madras 10, India A controlled clinical trial of trifluperidol on a group of chronic schizophrenic patients. *Current Therapeutic Research.* 14(1):17-21, 1972.

A controlled clinical trial of trifluperidol (compared with trifluoperazine) was carried out on 60 chronic schizophrenic patients. It consisted of 4 stages: 1) screening and selection; 2) period of observation without drug; 3) random allotment

of patients to trial groups; and 4) Q.P.S.S.and the Wings behavior rating scale were employed. The results were analyzed using analysis of variance technique. Highly significant improvement was noticed with patients on trifluperidol and trifluoperazine. No statistically significant difference in the therapeutic effect between these 2 drugs was noticed. Trifluperidol is a powerful neuroleptic with alerting and activating effects comparable to trifluoperazine. 5 references. (Author abstract modified)

110249 Ban, Thomas A. McGill University, Montreal, Quebec, Canada Schizophrenia: a psychopharmacological approach. Springfield, Ill., Charles C Thomas, 1972, 116 p.

Development of psychopharmacological methods, providing new means for therapeutically influencing and systematically studying schizophrenic psychopathology, has led to reassessment of instruments and points of reference in psychiatry. The new approach discussed is applied to problems related to schizophrenia and in the analysis and description of changes in schizophrenic patients brought about by the introduction of new drugs. The first section provides information on new drugs with antipsychotic properties; the second describes their effect on schizophrenic patients; and the final section discusses gradual change in current concepts of schizophrenia.

111340 Janssen, Paul; Brugmans, Jo; Dony, Jean; Schuermans, Viviane. Janssen Pharmaceutica, Research Laboratoria, B-2340 Beerse, Belgium An international double-blind clinical evaluation of pimozide. *Journal of Clinical Pharmacology and New Drugs.* 12(1):26-34, 1972.

Pimozide, a prototype of the diphenylbutylpiporidine series was studied in an international collaborative trial using standard protocols. The trial involved 180 chronic schizophrenic patients studied in 36 psychiatric institutions. All 180 patients had shown signs of clinical deterioration within 4 weeks of withdrawal of classical maintenance neuroleptic treatment and had improved after reinstitution of classical neuroleptics. Pimozide, in a single daily dose and as the sole drug was substituted for classical medication. Of 154 patients who improved markedly, 141 entered a placebo controlled double-blind study: 84 of them relapsed within the predicted 4 weeks of discontinuation of pimozide. Statistical analyses of the 36 item rating scales for the 84 patients who completed the study successfully and the 26 patients who deteriorated during pimozide treatment showed that pimozide produced additional benefits in patients who were sensitive to the antipsychotic and socializing effects of classical neuroleptics, whereas patients who did not respond to the incisive effects of neuroleptics but presumably benefited from their restraining or sedative effects deteriorated when treated with pimozide. Pimozide appeared to be the drug of choice for long-term maintenance treatment. 21 references. (Author abstract modified)

111554 Ayd, Frank J., Jr. 912 West Lake Avenue, Baltimore, Md. 21210 Neuroleptic therapy for chronic schizophrenia. *Diseases of the Nervous System.* 33(1):35-39, 1972.

Neuroleptic therapy for chronic schizophrenia is discussed and data from studies of phenothiazine, trifluoperazine, and chlorpromazine treatment are summarized. In treating chronic schizophrenia, the physician must guard against underdosage and overdosage and protect patients from the potential hazards of neuroleptics. In a clinical trial of a new neuroleptic in chronic schizophrenia, it is possible to make an effective drug appear ineffective or toxic or to make an ineffective drug appear efficacious or safe depending on the patients selected for the trial and the design of the trial. Despite the availability of a number of antipsychotically active neuroleptics, it is apparent that many schizophrenics, especially chronic schizophrenics, are not being properly treated with these drugs. Since the incidence of schizophrenia is about 1% of the world population, one of the most urgent tasks for drug research is the development of safer, longer acting, and more effective compounds for the maintenance therapy of chronic schizophrenia. 5 references.

114583 Climo, Henry J.; Billett, Bernice. no address Piperacetazine in chronic schizophrenia. *Journal of the Florida Medical Association.* 59(3):33-36, 1972.

Ten mental patients, 9 of them chronic schizophrenics, who had not responded satisfactorily to multiple therapy of potent psychotropic agents were placed on piperacetazine, alone, for a period of 12 weeks. The condition of 1 patient worsened, 1 was dropped for medical reasons, 2 showed good improvement, and 6 had excellent

results. In 7 patients, the previous extrapyramidal side effects disappeared and only one patient required continued antiparkinson medication. This preliminary study indicates that piperacetazine may be an important addition to the armamentarium of psychotropic drugs. 1 reference. (Author abstract)

114771 Sato, Mitsumoto; Uefuji, Keiko; Kuroda, Kunihiko. Okayama University, Medical School, Japan Stupor with continuous slow wave in EEG. ***Clinical Psychiatry (Tokyo).*** **14(1):23-31, 1972.**

A report on stupor with continuous slow wave in EEG is presented. The patient was a 22-year-old unmarried schizophrenic woman with functional stupor which appeared repeatedly and episodically for several hours to three days. Administration of amobarbital and diazepam immediately eliminated the slow wave train and stupor and generated alpha waves. However, bemegride and lucidril did not show any effect. A bibliographical review on the relationship between the slow wave train and stupor is presented. The stupor is considered to be induced by abnormal excitatory process in the inhibitory mechanism of the brain stem. 14 references.

115587 Denber, Herman C.B.; Turns, Danielle. Research Division, Manhattan State Hospital, Wards Island, NY Double blind comparison of thiothixene and trifluoperazine in acute schizophrenia. ***Psychosomatics.*** **13(2):100-104, 1972.**

Thiothixene was compared with trifluoperazine in a double-blind treatment trial in female acute schizophrenic patients. Although the drugs are considered to be equipotent, the final average dose of thiothixene was lower than that of trifluoperazine. Despite this dosage difference, the overall improvement rate for thiothixene was better than for trifluoperazine. Side effects were similar in both groups. The Inpatient Multidimensional Psychiatric Scale data analyses indicated a greater number of favorable changes with thiothixene. 8 references. (Author abstract)

115588 DiMascio, Alberto; Demirgian, Edward. Psychopharmacology Research Laboratory, Boston State Hospital, 591 Morton Street, Boston, MA 02124 Study of the activating properties of thiothixene. ***Psychosomatics.*** **13(2):105-108, 1972.**

Data are presented to provide objective substantiation of the clinical impressions of an activating property of thiothixene, observed in the treatment of hospitalized psychotic patients. Analyses of work output data showed that those patients continued on their previously prescribed medications showed a slight lowering of output over the course of the experimental four month period. In contrast, patients switched to thiothixene showed a gradual and continuing increase in output. It is suggested that with a longer course of thiothixene therapy, the output rate curve could have achieved a level sufficient for discharge and rehabilitation toward industrial employment. This activation may have resulted either indirectly, from an increase in the patients' level of motivation or, directly, from some motor stimulating property of the drug. Sophisticated research techniques should be employed to attempt a discrimination between these two modes of action. Finally, due to the low level of functioning of chronic schizophrenic patients in general and the consequent difficulty in rehabilitating them, the success of this drug in increasing their level of aspiration or actual achievement makes it a valuable therapeutic tool. 7 references. (Author abstract modified)

115591 Bianco, Fernando J.; Lerro, Furey A. Psychiatry Department, Temple University School of Medicine, Philadelphia, PA 19140 Schizophrenic syndrome, thyrotoxicosis and haloperidol. ***Psychosomatics.*** **13(2):120-121, 1972.**

A case history is presented of a patient with well known hyperthyroidism whose disease was poorly controlled and who, in a period of 13 months, had two episodes of thyrotoxicosis with associated schizophrenia like syndrome. During the second episode, chlorpromazine was used and worsened her status, while haloperidol helped remarkably. Propranolol proved to be ineffective in controlling psychiatric manifestations. No further use of psychotropic drugs was necessary after her thyroid dysfunction normalized. 8 references. (Author abstract modified)

115961 Toru, M.; Shimazono, Y.; Miyasaka, M.; Kokubo, T.; Mori, Y.; Nasu, T. Dept.of Neuropsychiatry, Tokyo Medical and Dental Univ., Tokyo, Japan A double-blind comparison of sulpiride with chlorpromazine in chronic schizophrenia. ***Journal of Clinical Pharmacology and New Drugs.*** **12(5,6):221-229, 1972.**

Clinical effectiveness of sulpiride in the treatment of chronic schizophrenia was compared with that of chlorpromazine as standard drug. Seventy

six hospitalized schizophrenics were paired from any group of three major types stratified as follows: patients with hallucinations and/or delusions, stupor or psychomotor excitement, and apathy and/or lack of spontaneity. Global comparative judgment of the effectiveness after an eight week administration period showed that sulpiride was more effective than chlorpromazine in 23 pairs. The latter drug was more effective than the former in 13 pairs. A significant difference was not found in the sequential analysis. Of the 58 patients who showed improvement, 34 were on sulpiride, the difference between both drugs being significant. Four patients on sulpiride and 13 on chlorpromazine showed no clinical improvement. Side effects appeared to be similar in kind and frequency for both drugs. No important effect on laboratory findings resulted from either drug. 11 references. (Author abstract modified)

116414 Saletu, B.; Saletu, M.; Itil, T.M.; Marasa, J. Missouri Institute of Psychiatry, University of Missouri, Columbia, MO The relationship between somatosensory evoked potential and quantitatively analyzed EEG during psychotropic drug treatment. *Psychophysiology.* 9(2):276, 1972.

In a paper presented to the Eleventh Annual Meeting of the Society for Psychophysiological Research the relationship between somatosensory evoked potential and quantitatively analyzed EEG during psychotropic drug treatment in schizophrenic patients was reported. The drug induced changes in somatosensory evoked potential (SEP) measurements in correlation with both EEG digital computer period analysis and analog power spectrum analysis measurements were investigated. Twenty seven chronic schizophrenic patients were recorded after eight weeks of placebo administration, and during the 12th week of treatment with major tranquilizers. Simple correlation analysis showed that a drug induced increase in SEP latency was correlated with decreases in EEG average frequency, frequency deviation, and fast beta activity, as well as with increases in alpha activity and amplitude variability (period analysis measurements). In regard to power spectrum analysis data, an increase of power in the theta and alpha bands was correlated with an increase of SEP latency and amplitude, whereas an increase of power in the beta bands was related to an amplitude decrease. (Author abstract modified)e

116833 Pishkin, Vladimir. Veterans Administration Hospital, Oklahoma City, OK Concept identification and psychophysiological parameters in depressed schizophrenics as functions of imipramine and nialamide. *Journal of Clinical Psychology.* 28(3):335-339, 1972.

The effects of imipramine and nialamide on cognitive and electrodermal (GSR) parameters of information processing in chronic schizophrenics who were characterized as demonstrating predominantly depressive features were studied. The Ss performed on concept identification (CI) tasks that varied in complexity; concomitant meaures of electrodermal activity were obtained. Major findings were: 1) both antidepressants facilitated CI performance; 2) there was a negative relationship between CI errors and spontaneous galvanic skin responses (GSRs); 3) the placebo Ss produced the least and the nialamide Ss the most GSRs; 4) CI errors increased monotonically with increasing problem complexity in the antidepressant groups, but not in the placebo condition. It was concluded that both imipramine and nialamide facilitate cognitive functioning of depressed schizophrenics. 11 references. (Author abstract modified)

116850 Serafetinides, E.A.; Willis, D.; Clark, M.L. Department of Psychiatry, School of Medicine, University of California, Los Angeles, CA 90024 EEG dose-response relationships of chlorpromazine in chronic schizophrenia: the effects on the various rhythms and on alpha blocking. *Biological Psychiatry.* 4(3):251-256, 1972.

EEG dose response relationships of chlorpromazine in chronic schizophrenia were studied in a group of 31 female patients. EEG studies were conducted monthly in a six month chlorpromazine (CPZ) dose response, double-blind, placebo controlled trial. Of the 31 patients, five were on placebo, six on 150 mg/day CPZ, seven on 300 mg/day CPZ, and thirteen on 600 mg/day CPZ. Despite the small number of the samples involved some significant EEG dose response relations were found, consisting mainly in more and slower alpha rhythm in the higher medication groups, and conversely, more beta rhythm in the lower medication groups. The EEG changes on the whole were far less obvious than reported in the literature and some of the reasons were discussed. 20 references. (Author abstract modified)

116854 Alias, A.G.; Vijayan, N.; Nair, D.S.; Sukumaran, M. Department of Biochemistry, Medical College, Calicut, S.India Serum ceruloplasmin in schizophrenia: significant increase in acute cases especially in catatonia. *Biological Psychiatry.* 4(3):231-238, 1972.

Serum ceruloplasmin activity was measured in 51 relatively acute cases (of usual types) and 44 chronic cases (of usual types) of patients with schizophrenia, and in 55 healthy normal subjects, using p-phenylenediamine oxidation. Most of the patients and the normals were males. No appreciable sex difference in the ceruloplasmin values was noted in either normals or schizophrenics. Analysis of variance showed that the ceruloplasmin values of normals and of chronic cases were almost the same, and that the values of acute cases are different from (higher than) those of the former groups. Among the acute cases, acute catatonic stupor cases gave values consistently in the highest range. The possible mechanism of the increase in acute cases is discussed. Whole blood ascorbic acid was estimated in 35 schizophrenics (22 acute and 13 chronic cases) and 19 normals, using 2,4-dinitrophenylhydrazine. The graphs plotting the ascorbic acid values against the corresponding ceruloplasmin values did not show any relationship between the two values. 28 references. (Author abstract)

116904 Saletu, B.; Itil, T.M. Department of Psychiatry, University of Missouri, Columbia, MO Thiopental activation and spontaneous sleep and dream patterns of resistant schizophrenics. *Canadian Psychiatric Association Journal (Ottawa).* 17(Special Supplement 2):209-219, 1972.

A panal discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which thiopental activation and spontaneous sleep and dream patterns of resistant schizophrenics are described. Thiopental activated EEGs, spontaneous sleep EEGs and dream patterns were studied in 48 chronic schizophrenic patients who were retrospectively divided into a therapy resistant and responsive group in terms of therapeutic outcome. Using an analogue frequency analyzer it was found that therapy resistant subjects exhibited more power in the slow frequency bands and less power in the fast frequency bands than did responsive subjects during both resting recordings and thiopental postnarcotic sleep. The spontaneous all night sleep investigations yielded similar findings. Digital computer sleep prints demonstrated that resistant schizophrenics had longer periods of deep sleep and fewer awakening states than did responsive patients, whereas responsive patients exhibited more REM activity. Evaluation of the digital computer period analysis measurements during all night sleep revealed that 0-8 cps activity appeared to a greater extent in therapy resistant schizophrenics, while over 8 cps activity was predominant in the responsive group of patients. The clinical significance of these findings is discussed, with the conclusion that quantitative electroencephalography may be a valuable instrument in predicting the therapy responsiveness of a schizophrenic population. 28 references. (Author abstract modified)

117028 Johnson, D.A.W.; Freeman, Hugh. University Hospital of South Manchester, England Long-acting tranquillizers. *Practitioner (London).* 208(1245):395-400, 1972.

A within patient comparison of schizophrenics who were prescribed oral phenothiazines (fluphenazine) on a long-term basis and the same patients placed on a regimen of injections of long-acting phenothiazines is reported. Fluphenazine resulted in a reduction in the frequency of readmission and the total length of hospital stay. It is suggested that the injection regimen makes the relapses which did occur less severe. 16 references.

118516 Wyatt, Richard; Vaughan, Tom; Dawson, Susan; Green, Richard; Kaplan, Jonathan. Laboratory of Clinical Psychopharmacology, National Institute of Mental Health, Rockville, MD High dosages L-5HTP administration in phenothiazine resistant chronic schizophrenic patients. (Unpublished paper). Washington, DC, NIMH, 1972, 1 p.

Eleven male chronic schizophrenics were administered placebo (one month), L-5HTP up to 6gm/24 hr and MK-486 (a peripherial decarboxylase inhibitor 150mg/24 hr) for up to three months and a second one month of placebo. When compared to placebo, seven patients improved, two became worse, and for two there was no change in behavior. Each patient's sleep, eight hours a night, during each placebo period and during five drug dosage ranges was studied. Usable 5HTP sleep data was obtained from eight of the 11 patients. The most consistent findings was

an increase in REM latency from a mean of 57 to 138 minutes with 1500mg/24 hr 5HTP. The REM latency increased further to 170 minutes with 6000mg/24 hr. There was a decrease in mean REM percent from 22% to 15% on 1500mg which did not further decrease on higher 5HTP dosages. There were no consistent changes in total sleep, REM density, delta sleep, or sleep latency. There were large individual differences, however, in some of these measurements which may be related to dosage and clinical response. A larger sample of patients is needed to determine this. (Author abstract modified)

118524 Kaplan, Jonathan; Vaughan, Tom; Dawson, Susan; Green, Richard; Wyatt, Richard J. Laboratory of Clinical Psychopharmacology, National Institute of Mental Health, Washington, DC Effect of chlorpromazine on the sleep of ten chronic schizophrenics. (Unpublished paper). Washington, DC, NIMH, 1972.

The effect of chlorpromazine on the sleep of ten male chronic schizophrenics was studied. Patients were kept phenothiazine free for a period of three weeks to five months before placebo sleep data were obtained. Similarly, during the drug period they were given 400mg chlorpromazine daily for at least three weeks prior to data collection. Their sleep was studied eight hours a night for six nights during drug and placebo periods. Data from nights in which total sleep was under 100 minutes was not used. Chlorpromazine produced a significant increase over placebo in REM density and delta sleep time when the mean values for each patient were compared. In addition, there was an indication that total sleep was increased. There was generalized disruption in sleep during both periods compared to figures for normal subjects, however, chlorpromazine produced no significant differences in sleep latency, REM latency, REM time, or REM percent. Although chlorpromazine does not drastically alter the sleep patterns measured of chronic schizophrenics eye movements are more concentrated during the REM period. Slow wave sleep, although still well below normal, was increased. (Author abstract)

09 DRUG TRIALS IN AFFECTIVE DISORDERS

100978 Shearer, Lloyd author address not given Salt of tranquility. *Washington Post.* February 20, 1972. Parade, p.20.

An editorial announces the newly attempted, successful use of an inexpensive salt derived from lithium for treatment of manic and depressive mental disorders. It is claimed to be more effective than conventional tranquilizers, antidepressants or shock treatments. A 2 year study in 4 British hospitals reports 24 of 28 improved cases among patients observed. Cost averages $25.per patient per year.

110017 Davies, Brian; Carroll, Bernard J.; Mowbray, Robert M. Royal Melbourne Hospital, Victoria, Australia Depressive illness: some research studies. Springfield, Ill.; Charles C Thomas, 1972. 456 p.

Investigations of the hypothalamic pituitary adrenal axis in depressed and control patients are described. Studies of the 5-hydroxy indoleacetic acid content of cerebrospinal fluid of depressed and control subjects are reported, as is a sequential therapeutic trial of l-tryptophan and electroconvulsive therapy in severely depressed patients. Measurement of depression and applications of multivariable analysis to the problems of classifying the depressive syndrome are discussed, and studies in general practice are described.

112136 Schildkraut, Joseph J. Harvard Medical School, Boston, Massachusetts Neuropharmacological studies of mood disorders. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p. (p.65-84)

Two aspects of neuropharmacological studies of mood disorders are reported. Some of the data are presented on the effects of imipramine and other tricyclic antidepressants on the turnover and metabolism of norepinephrine in the animal brain. Emphasis is given to the finding that the effects of acute and chronic administration of imipramine on norepinephrine turnover are different, as the differences may help to explain the need for chronic administration of tricyclic compounds in order to obtain clinical antidepressant effects. Some of the findings are then summarized from clinical studies of norepinephrine metabolism in patients with affective disorders. 45 references.

112142 Fieve, Ronald R. New York State Psychiatric Institute, New York Lithium studies and manic-depressive illness. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p.(p.135-145).

Important current issues in lithium studies as related to manic-depressive illiness are reviewed, with emphasis on 2 particular areas: 1) lithium's current status as a prophylactic agent in depression, and 2) the clues that are available as to lithium's biochemical mode of action. Some of the studies originating at the New York State Psychiatric Institute are noted and a limited number of related key contributions from other investigators reviewed. Known facts about lithium's therapeutic effectiveness is mania, schizoaffective illness, and depression are summarized, followed by a consideration of the prophylactic question. 44 references.

112143 Shopsin, Baron. New York University Medical Center, New York /Lithium studies and manic-depressive illness./ Discussion of Dr.Fieve's paper. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p.(p.146-150).

Fieve's paper on the problem of lithium as a prophylactic agent for depression is summarized and evaluated, with additional data offered on other studies. It is concluded that the problems and deficiencies in assessing the scientifically valid activity of lithium are manifold and more clear than the answers sought. The problems that make both research design and evaluation of published data difficult are: 1) differential diagnosis; 2) rarity of manic-depressive illness; 3) cyclicity and the inherent factor of high incidence of spontaneous remission; 4) management problems associated with manic patients and their effect on design; 5) previous and concomitant use of other psychoactive drugs; 6) lack of specific and relevant psychiatric rating devices for mania and rare usage of the existing ones in the studies reported; and 7) the almost complete lack of control studies with other so-called established psychoactive compounds.

112146 Klerman, Gerald L. Harvard Medical School, Boston, Massachusetts Clinical research in depression. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p.(p.165-193).

Current trends in clinical research in depression are reviewed as they reflect the new findings from antidepressant drug therapies and the neuropharmacological and biochemical discoveries related to their actions. Special attention is given to problems in clinical diagnosis and classification of depression. The historical background of clinical thinking about the nature and characterization of depression is mentioned. Some recent studies of endogenous depression are examined, particularly as they relate to differential prediction of treatment, and problems in research methodology and clinical theoretical thinking are highlighted. 59 references.

113341 Herring, Fred H.; Katz, George; Mason, Donald J. Veterans Administration Hospital, Denver, Colorado Hyper-manic states: schizoaffective and/or a 'true' manic-depressive state. *Newsletter for Research in Psychology.* 14(1):32-33, 1972.

Behavioral syndromes of schizoaffectives and 'true' manic depressives were found to be dichotomized in an admittedly small local sample. Schizoaffectives had current or historical evidence of hallucinations, delusions and a thought disorder, while a remarkably smaller group of 'true' manic depressives had none of these, excepting delusions of grandiosity. In particular, the psychological test data clearly differentiated the 2 groups on, not a continuum, but the presence or absence of signs of a thought disorder, adequate ego strength, contact with reality, etc. The importance of the study stems, in part, from the possibility that lithium carbonate treatment may be effective only in the manic depressive state, and may actually be deleterious to schizoaffective patients.

113376 Bowers, Malcolm B., Jr. The Connecticut Mental Health Center, 34 Park St., New Haven, Conn. 06508 Cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) following probenecid in unipolar depressives treated with amitriptyline. *Psychopharmacologia (Berlin).* 23(1):26-33, 1972.

Lumbar cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), and the ratio 5HIAA/HVA were measured following probenecid administration in 11 patients with unipolar depression before and during treatment with amitriptyline (AMI). Control values were obtained from a group of inmate volunteers. Prior to treatment CSF 5HIAA formation in the depressives was not different from controls. During treatment with AMI,CSF 5HIAA formation decreased. One patient with psychotic symptoms prior to AMI and 2 patients who developed psychotic reactions on AMI showed relatively low CSF 5HIAA formation prior to an-

tidepressant therapy. Compared to controls CSF HVA values were higher in the depressives prior to AMI therapy. 23 references. (Author abstract modified)

114026 Tucker, Walter I.; Bell, George O. 605 Commonwealth Avenue, Boston, Massachusetts 02215 Effectiveness of lithium carbonate in the prevention of manic and depressive episodes. ***Medical Clinics of North America.*** **56(3):681-686, 1972.**

The effectiveness, safety, and practicability of prophylactic lithium carbonate treatment in office and general hospital practice in the prevention of manic and depressive episodes are indicated. The results are based on experience in the treatment of private patients, indicating minimum risk. Patients were selected who had had frequent mood swings, usually with rapid changes over weeks or months, with manic-depressive reactions constituting the largest group. The treatment was found to be quite safe when contact is maintained with the patient and the established guidelines regarding dosage, blood level, and intercurrent illness are followed. 8 references.

115186 Laird, S.M.; Sage, M. Plastic and Reconstructive Surgery Centre, St.Lawrence Hospital, Chepstow, Monmouthshire, Wales Psychosis and ketamine. ***British Medical Journal (London).*** **1(5794):246, 1972.**

In a letter to the editor the use of ketamine anesthesia in a patient suffering from psychotic depression in the puerperal period after the birth of her second child is reported. Ketamine can be used with its distinct advantages in patients who are mentally ill. It is necessary to use a premedication and to avoid overdosage with the drug. Postoperative sedation is probably advisable in these cases.

115590 Bodnar, S.; Catterrill, T.B. Department of Obstetrics and Gynecology, Queen Elizabeth Hospital, Montreal, Quebec, Canada Amitriptyline in emotional states associated with the climacteric. ***Psychosomatics.*** **13(2):117-119, 1972.**

The general nature of changes in climacteric phases is briefly discussed, along with psychopharmacological methods for treating such conditions. It is stressed that: 1) the emotional state associated with the climacteric is an exhaustion reaction in the face of endocrine, metabolic and psychological readjustment. 2) The emotional changes are of multifactorial etiology, and the climacteric may only accentuate a preexisting insufficiency. 3) Amitriptyline has a justified place in the treatment of emotional upsets associated with the climacteric. Its success - failure rate and low percentage of side effects support this opinion. Patients can be treated on an ambulatory basis, with no interruption of work. 4) Clear cut somatic vasomotor changes are more effectively treated with estrogen compounds. 5) Society's structure and set of values will increase the number of patients who will seek medical advice for emotional changes at the time of the climacteric. 12 references. (Author abstract modified)

116386 Kishimoto, Akira; Nakao, Takehisa; Okuma, Teruo; Komatsubara, Takayoshi. Department of Neuropsychiatry, Tottori University School of Medicine, Japan Occurrence of generalized convulsions in lithium therapy -- a case report. ***Clinical Psychiatry (Tokyo).*** **14(1):57-63, 1972.**

A case of a 14-year-old female manic-depressive who experienced generalized convulsions after lithium therapy is reported. The patient was administered psychotropic drugs of phenothiazine derivatives, LiC03 at doses of up to 1,350mg and electro shock therapy. The patient had generalized convulsions three times successively 34 hours after termination of LiC03. Decrease in volition and slowdown of brain waves were observed for eight months after the convulsions. They gradually disappeared however along with the manic-depressive symptoms. 25 references.

116534 Mendlewicz, J.; Fieve, R.R.; Stallone, F.; Fleiss, J.L. New York State Psychiatric Institute, Columbia University, New York, NY 10027 Genetic history as a predictor of lithium response in manic-depressive illness. ***Lancet (London).*** **1(7750):599-600, 1972.**

Genetic history as a predictor of lithium response in manic-depressive illness was considered in a family study of all patients admitted to a double-blind trial of lithium prophylaxis. The data for the first 78 weeks were analyzed for four samples of patients: responders and failures under lithium and responders and failures under placebo. Response to lithium was significantly correlated with the presence of bipolar illness in the proband's first and second degree relatives. No association was found between family history and response to placebo. 8 references.

118075 Post, Robert M.; Gillin, J.Christian; Goodwin, Frederick K.; Wyatt, Richard J.; Snyder, Frederick. Laboratory of Clinical Sciences, NIMH, Bethesda, MD 20014 The effect of orally administered cocaine on sleep of depressed patients. Rockville, Md., NIMH, 1972. 1 p.

The clinical and physiological effects of orally administered cocaine on sleep of depressed patients are reported. Five trials of cocaine were given to four depressed patients. Two male bipolar patients and two female unipolar patients were given starting oral doses of 30-60mg cocaine per day and increased to 60-185mg at the end of a four to seven day trial. Baseline sleep recordings were obtained during a drug free placebo period before and after cocaine administration. Cocaine significantly reduced REM sleep time compared with pretrial and rebound periods. Other trends in the data suggested that cocaine had a generally disruptive effect on sleep, but the differences in these parameters did not reach statistical significance in this small sample. The ability of cocaine in these patients to produce a reduction of REM with subsequent withdrawal rebound is consistent with the effects of most psychically or physiologically addicting drugs and with those that block reuptake of norepinephrine and serotonin. The effect on sleep is of particular interest in that cocaine at doses employed in this study did not cause changes in vital signs or consistent alteration of clinical state, yet provides evidence that orally administered cocaine is absorbed and physiologically active in the central nervous system.

118076 Gillin, J.C.; Kotin, J.; Post, R.; Wyatt, R.J.; Snyder, F.; Goodwin, F.K. NIMH, Bethesda, MD 20014 Sleep during one week of administration of delta(9)-tetrahydrocannabinol to psychiatric patients. Rockville, Md., NIMH 1972. 1 p.

The effects of delta(9)-tetrahydrocannabinol (delta(9)-THC) on depressed psychiatric patients is reported. All night sleep recordings were obtained from three depressed male psychiatric inpatients during a double bind therapeutic trial of delta(9)-THC. The patients were given two nights to adapt to sleep recordings, then they were studied for a three day placebo period, a five to seven day period of delta(9)-THC administration of 0.3mg/kg, and then for two placebo nights. No consistent effects were noted in total sleep, RT, NREM, REM, REM%, REM latency, and sleep latency. The only consistent change, noted on all three patients, was a reduction in REM time the first night of drug administration. More longitudinal studies are in progress and will be reported later.

10 DRUG TRIALS IN NEUROSES

108149 Hoehn-Saric, Rudolf; Liberman, Bernard; Imber, Stanley D.; Stone, Anthony R.; Pande, Shashi K.; Frank, Jerome D. Room 124, Phipps Clinic, Johns Hopkins Hospital, Baltimore, Md. 21205 Arousal and attitude change in neurotic patients. *Archives of General Psychiatry.* 26(1):51-56, 1972.

Two groups of neurotic patients were subjected to identically highly dramatic treatments and both were led to expect some change in their conditions. Twenty Ss were treated: one half were aroused by ether inhalation and one half were kept in a state of low arousal through premedication with chlorpromazine. Short-term attitude changes, measured on Osgood's Semantic Differential, were comparable for both groups during the first session but were significantly greater for the aroused group during the subsequent session, indicating that in influencing patients persuasive circumstances were less effective alone than when combined with arousal. 28 references. (Author abstract modified)

108155 Uhlenhuth, Eberhard H.; Covi, Lino; Rickels, Karl; Lipman, Ronald S.; Park, Lee C. Dept.of Psychiatry, Univ.of Chicago, 950 E.59th St., Chicago, Ill. 60637 Predicting the relief of anxiety with meprobamate: an attempt at replication. *Archives of General Psychiatry.* 26(1):85-91, 1972.

Nonpharmacologic factors affecting anxiety relief were compared in 2 independent samples of psychoneurotic patients treated 4 or 6 weeks with meprobamate or placebo. Patient reports of anxiety relief were analyzed with respect to medication, some 20 characteristics of patient and treatment, and the interaction of medication with each characteristic. The results indicate that anxious neurotic outpatients who are Black and better educated are likely to respond best to the act of pill taking in general, whereas the specific pharmacologic effect of meprobamate is likely to be most helpful with patients who are older and less enthusiastic about pill taking. Patients taking meprobamate improved more in one sample, whereas patients taking placebo improved more in the second sample. The effect of more ex-

perienced therapists in the second sample probably washed out the effect of meprobamate in that sample. 18 references. (Author abstract)

108406 Weissman, Myrna M. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut Casework and pharmacotherapy in treatment of depression. ***Social Casework.*** **53(1):38-44, 1972.**

Experiences with 40 depressed outpatients receiving casework treatment in conjunction with antidepressant medication from a psychiatrist are described. Focus is on the problems arising from combining casework with pharmacotherapy. The kind of casework intervention depends on the patient's symptomatic state, personality and interest. Casework with acutely symptomatic patients is primarily supportive. Patients with overt social and interpersonal problems tend to be interested in casework treatment, patients with more stable social problems are less interested in casework. Patients who are negative to casework tend to show negativism to medication and psychiatry as well. Problems associated with combining casework with pharmacotherapy arise out of the divergent goals of each treatment. The caseworker's close collaboration with the psychiatrist is necessary to resolve potential professional conflicts. 10 references. (Author abstract modified)

108807 Rickels, K.; Hutchison, J.; Morris, R.J.; Csanalosi, I.; Parsia, K.; Pereira-Ogan, J.A. 203 Piersol Bldg., University Hospital, 3400 Spruce St., Philadelphia, Pa. 19104 Molindone and chlordiazepoxide in anxious neurotic outpatients. ***Current Therapeutic Research.*** **14(1):1-9, 1972.**

The therapeutic efficacy of molindone was slightly less than that of chlordiazepoxide in a controlled study of 148 patients with neurotic anxiety. Clinic patients were less improved than GP patients. There were no drug versus population interaction effects. More sedation was noted with chlordiazepoxide than with molindone, but other side effects were similar for both drugs. 9 references.

111295 Schuster, Timothy S.; Winslow, Walter W.; Kellner, Robert. Department of Psychiatry, School of Medicine, University of New Mexico, Albuquerque, New Mexico A comparison of thioridazine and diazepam in non-psychotic anxiety-depression: a pilot study. ***Current Therapeutic Research.*** **14(3):131-135, 1972.**

A preliminary comparison of the effectiveness of diazepam and thioridazine in a group of nonpsychotic patients who were anxious and depressed is reported. During the study there was a conspicuous reduction in scores in anxiety and in depression on most measures for both groups and several of the changes in scores reached a significant level. There was a tendency for a greater reduction in scores of anxiety and depression with thioridazine than with diazepam. The Multiple Affect Adjective Check List tended to discriminate less effectively between the 2 groups than the other scales used and tended to show also smaller changes during the study. No definite conclusions can be drawn from the results of this pilot study about the relative efficacy of thioridazine and diazepam in view of the large number of dropouts and in view of the differences between the 2 groups at the beginning of the trial. 9 references. (Author abstract modified)

115162 Tupin, Joe P. Dept.of Psychiatry, University of California School of Medicine at Davis, Davis, CA Lithium use in nonmanic depressive conditions. ***Comprehensive Psychiatry.*** **13(3):209-214, 1972.**

The effect of lithium on clinical conditions other than the various phases of manic-depressive illness was reviewed. Lithium gave a favorable response with the schizo -affective disturbances, childhood disorders, premenstrual tension, cyclothymic personality, paranoid reaction, epilepsy, obsessive states, catatonia and explosive aggressive personality disorders. Poor results were reported for phobias and alcoholics. The following general hypotheses were suggested: (1) lithium is not specific for manic-depressive depressive illness, but acts favorably in a variety of clinical conditions characterized by aggressiveness and/or an episodic course; (2) aggressiveness and the episodic course have biologic roots, while the final clinical expression varies because of unique, individual psychosocial experiences; (3) the postulated biological abnormalities of aggression and periodicity ((episodic course) may be interrelated as drive and control mechanism, respectively. 41 references.

115589 Grozier, Michael L. Squibb Institute for Medical Research, Princeton, NJ 08540 Motival in the treatment of anxiety, with or without depression. ***Psychosomatics.*** **13(2):109-116, 1972.**

The clinical testing of Motival, a formulation of fluphenazine and nortriptyline, as a useful

psychotropic drug in the treatment of anxiety, with or without the existence of depression, is reported. Motival-10 and Motival-20 were shown to be effective in the treatment of outpatients with mild to moderate anxiety, with or without concomitant depression. In a series of double-blind controlled clinical trials, Motival-10 and Motival-20 were equal to or superior to most of the psychotropic agents commonly used in patients of this type. In no case was another drug shown to be superior to Motival. In addition, Motival was shown to be safe, with an incidence of adverse effects comparable to or less than that for its components, or for the drugs with which it was compared. Motival is thought to be more effective than the other agents with which it was compared, because it possesses a broad spectrum of activity not only against the symptoms and manifestations of anxiety, but also against those of depression. Neither of the components of Motival, fluphenazine or notriptyline, has been reported to cause drug abuse. (Author abstract modifiec)

115592 Kerry, R.J.; Jenner, F.A.; Pearson, I.B. Northern General Hospital, Sheffield, England A double blind cross over comparison of RO5-3350, Bromazepam, diazepam (Valium) and chlordiazepoxide (Librium) in the treatment of neurotic anxiety. *Psychosomatics.* 13(2), 122-124, 1972.

A double-blind cross over comparison was made of RO5-3350 (Bromazepam), diazepam (Valium) and chlordiazepoxide (Librium) in the treatment of neurotic anxiety. It is stressed that chlordiazepoxide and diazepam have established themselves as active therapeutic agents for the symptomatic relief of neurotic anxiety. They are safe in overdose and can be taken over long periods with safety. Statistically, RO 5-3350 is highly significantly better for the treatment of neurotic anxiety than chlordiazepoxide. This leads to the conclusion that the trial shows convincingly that RO 5-3350 is effective in reducing anxiety in neurotic patients. Its main disadvantage when used in a dose of 10 mgm t.i.d.is the significantly increased incidence of the unwanted effect of drowsiness and ataxia when compared with the other two drugs in the doses used in this trial. The drug seems to be safe and free from toxic effects and even after three years administration no abnormal blood or liver function tests have been obtained. It is efficacious for the treatment, (but not cure), of neurotic anxiety and does not appear to be specific for any symptom clusters. 5 references. (Author abstract modified)

115593 Naftulin, Donald H.; Ware, John E., Jr. University of Southern California School of Medicine, Los Angeles, CA 90033 A behavioral and clinical evaluation of two psychotropic agents: doxepin-hydrochloride and perphenazine-amitriptyline hydrochloride. *Psychosomatics.* 13(2):125-130, 1972.

In a double-blind experiment, the efficacy and side effects of doxepine-hydrochloride and perphenazine-amitriptyline HCL were studied in 40 outpatients diagnosed in the categories of anxiety-depression. It was found that: (1) a combination of perphenazine (2mg) and amitriptyline (25mg) seems to have a more rapid antidepressant action than doxepin-HCL (25mg) according to scores on the Zung Self-rating Depression Scale. Both groups showed a rapid lowering of anxiety scores, but it occurred faster in the group treated with doxepin-HCL. (2) Associated with the early differences between groups in amount of depression and anxiety is the observation that five subjects in the doxepin-HCL group reported depression as a complaint about that drug, whereas none in the perphenazine - amitriptyline groups, as contrasted with one in the doxepin group, complained of difficulty in concentrating. It appears that doxepin acts to reduce anxiety more rapidly than it does in depression. Although the results provide new evidence for the biphasic nature of these drugs, further research is required into their specific mechanism of action and effects. 5 references. (Author abstract modified)

115594 Goldberg, Harold L.; Nathan, Leon. West-Ros-Park Mental Health Center, Boston State Hospital, Boston, MA A double-blind study of Tofranil Pamoate vs. Tofranil A double-blind study of Tofranil Pamoate vs. Tofranil Hydrochloride. *Psychosomatics.* 13(2):131-134, 1972.

Two methods of administering Tofranil have been compared in a double-blind trial on 43 patients with primary depression, divided into two parallel treatment groups. Tofranil hydrochloride in doses of 25 mg.t.i.d.did not differ significantly from Tofranil pamoate in doses of 75mg.once daily for a six week period as measured by global assessment of depression, anxiety, and neurotic manifestations, and by a rating scale for depression (Lehmann-Rockliff scale). 5 references. (Author abstract)

115650 Weise, Charles C.; O'Reilly, Patricia P.; Hesbacher, Peter. Board of Education, Kanawha County Schools, 200 Elizabeth Street, Charleston, WV Perphenazine - amitriptyline in neurotic underachieving students: a controlled study. *Diseases of the Nervous System.* 33(5):318-325, 1972.

A double-blind controlled study comparing a combination agent consisting of perphenazine, a major tranquilizer, and amitriptyline, an antidepressant, with each of its constituents and placebo in neurotic underachieving students attending elementary school is presented. There was a differential effect of level of depression upon clinical and developmental improvement, a consistent and pervasive response to placebo during the eight weeks of treatment, and a failure to document any superiority for the combination perphenazine - amitriptyline over perphenazine or amitriptyline alone. The evidence suggests that the response to phenothiazine differs from tricyclic pharmacotherapy as a function of the kind of improvement desired, clinical or developmental. 17 references. (Author abstract modified)

117103 Gallant, D.M.; Bishop, M.P.; Guerrero-Figueroa, R. Tulane University Department of Psychiatry and Neurology, New Orleans, LA WIN 27,147-2: a preliminary evaluation of a potential antidepressant compound: animal and human correlations. *Current Therapeutic Research.* 14(2):61-64, 1972.

The antidepressant effect of WIN 27,147-2 (3-(dimethylamino) -1,2,3,4-tetrahydrocarbazole hydrochloride) was investigated in 11 male chronic alcoholic inpatients and cats presenting the symptamology of depression. The clinical data of WIN 27,147-2 strongly suggest that this compound does possess antidepressant properties. Although no definitive statement as to efficacy may be made (in the absence of a control group), WIN 27,147-2 produced a degree of improvement which at least parallels and may exceed that of other active antidepressant agents screened in this patient population. Also impressive is the virtual absence of side effects at dosage levels which appear to produce definite improvement. The drug certainly merits further study under controlled conditions. 5 references. (Author abstract modified)

117104 Park, Sanghae; Gershon, Samuel; Angrist, Burton; Floyd, Arthur. Neuropsychopharmacology Research Unit, Department of Psychiatry, New York Univ.Medical Center, 550 First Avenue, New York, NY 10016 Evaluation of an aminotetraline, CP 14.368, as an antidepressant. *Current Therapeutic Research.* 14(2):65-70, 1972.

CP 14.368 (N,N-dimethyl-5-methoxy-8-chloro-1,2,3,4,-tetrahydro-1-napthylamine), an aminotetraline derivitive was evaluated as an antidepressant in ten depressed patients in an open trial. Clinically, two patients attained moderate improvement, four minimal improvement, one no change, and three became worse. Nine patients had side effects. CP14.368 could not be considered an effective antidepressant, particularly with its high incidence of side effects in this study. However, further study in a homogenous group of endogenous depression is suggested. 9 references. (Author abstract modified)

118788 Forrest, W.A. Ciba Laboratories, Horsham, Sussex, England Anxiety in general practice: 10,703 patients treated with benzoctamine (Tacitin). A report of a monitored-release study. *Current Therapeutic Research.* 14(5):227-238, 1972.

A total of 10,703 patients in general practice, with a diagnosis of moderate to severe anxiety, often with depressive overtones, were treated with benzoctamine 10mg t.i.d.for three weeks. During this treatment period, 85%of the group obtained symptomatic relief, and 55% were symptomfree after three weeks. In this large group of patients, benzoctamine was well tolerated, 83% of the patients reporting no side-effects. Drowsiness was the most commonly reported adverse reaction with an incidence of 6.5%. The incidence of other side-effects was low and is comparable with those induced by placebo. 8 references. (Author abstract)

118789 McLeod, W.R. Department of Psychiatry, University of Auckland P.B., Auckland, New Zealand A comparison of diazepam, benzoctamine, and placebo in anxiety states. *Current Therapeutic Research.* 14(5):239-245, 1972.

After a double-blind crossover trial in which each of six patients acted as his own control, it was concluded that diazepam is superior to benzoctamine in the rapid relief of anxiety in patients in whom these symptoms have been present for several years. Benzoctamine in the dosages used (10mg and 20mg) did not differ from placebo but the possibility of more slowly developing anxiolytic action cannot be eliminated. 7 references. (Author abstract)

118822 Anderson, J.; Lambert, N.G.; Pigott, P.V. Department of Biomathematics, University of Oxford, Oxford, England An evaluation of fluphenazine with nortriptyline in anxiety and depression. *Practitioner (London).* 208(1246):511-517, 1972.

A study was made to evaluate the efficacy of Motival (a combination of fluphenazine and nortriptyline) in the treatment of patients exhibiting anxiety with mild depression. A double-blind evaluation on 100 outpatients was run for 28 days using perphenazine combined with amitriptyline (triptafen DA), Motival, and placebo. Four of five patients randomly received one of the combinations and the fifth received a placebo. One capsule was taken three times daily for four weeks. Patients were divided according to symptoms into three groups: mental and emotional, psychosomatic, and physiological functions; and were rated at day zero, day 14 and day 28. Results showed that: Motival and Triptafen each relieved the symptoms of both anxiety and depression; there was no evidence that either treatment was better; and response of the placebo group was consistently less marked in all parameters, especially in the patients' self-rating scores. The drug related side-effects were blurred vision, dry mouth, and constipation. 9 references.

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

112259 Pearlman, Chester A., Jr.; Sax, Daniel S.; Feldman, Robert D. Dept.of Psychiatry Research, VA Hospital, Boston, Mass. Psychiatric aspects of L-dopa therapy of Parkinson's disease. *Psychiatry in Medicine.* 3(1):45-50, 1972.

Psychiatric complications of L-dopa treatment of Parkinson's disease at a hospital were less frequent and severe than reported at other institutions. Psychosocial factors were much more prominent in the complications that did occur than a pharmacologic effect of L-dopa. Interest in the connections between L-dopa, catecholamine metabolism and emotional disorder should not lead to neglect of medical - psychological aspects of L-dopa therapy. 42 references. (Author abstract)

112668 Pearce, John. author address not given Reversal of hemiballismus by tetrabenazine. *Journal of the American Medical Association.* 219(10):1345, 1972.

A letter to the editor reports studies which suggest the dramatic relief of hemiballismus after treatment with tetrabenazine. It appears that a trial of tetrabenazine is merited in all such cases before proceeding to stereotactic surgery. Tetrabenazine may act by suppressing an increased sensitivity to normal levels of endogenous dopamine (and possibly serotonin), which develop as a result of a destructive lesion in the subthalamic nucleus or its efferent pathway. 10 references.

113168 Millichap, J.Gordon. 720 Michigan Avenue, Chicago, Illinois 60611 Drug treatment of convulsive disorders. *New England Journal of Medicine.* 286(9):464-469, 1972.

Drug treatment of convulsive disorders is reviewed, noting that the choice is dependent on the clinical pattern of the seizure and the electroencephalic abnormality. The clinical manifestations of seizures are classified in four groups: major (grand mal, status epilepticus, and infantile spasms), minor (petit mal, myoclonic seizures, and akinetic seizures), psychomotor, and focal. Drugs effective against major and focal seizures are outlined, followed by those effective against petit mal, psychomotor seizures, and status epileticus. General principles of anticonvulsant therapy are also set forth, with some emphasis on the duration of the therapy. 12 references.

113404 Hall, Colin D.; Weiss, Edward A.; Morris, Charles E.; Prange, Arthur J., Jr. Department of Medicine, University of North Carolina, Chapel Hill, N.C. 27514 Rapid deterioration in patients with parkinsonism following tryptophan-pyridoxine administration. *Neurology.* 22(3):231-237, 1972.

In a clinical trial involving 3 patients with parkinsonism, L-tryptophan was administered orally, first alone and then in conjunction with 100mg.of pyridoxine per day. There was no significant alteration in the clinical condition of the patients with L-tryptophan alone, but each showed marked and rapid deterioration with the addition of pyridoxine. Pyridoxine alone had no such effect. It is suggested that in certain disease processes dopamine may favor a hypotonic state while 5-hydroxytryptamine favors a hypertonic state and that the ratio of these 2 may be critical in movement disorders. 28 references. (Author abstract modified)

114484 Clements, Richard O. 4110 Durness Way, Houston, Texas Gilles de la Tourette's syndrome -- an overview of development and treatment of a case, using hypnotherapy, haloperidol, and psychotherapy. ***American Journal of Clinical Hypnosis.*** **14(3):167-172, 1972.**

A brief review of the literature is given concerning a nervous affliction characterized by motor incoordination, accompanied by echolalia and coprolalia and known as Gilles de la Tourette's syndrome. The development, course and treatment of a case of this syndrome is described in the case of a second born Jewish male. Data are included from the inception of the disturbance at age 4 and cover a 13 year period. Haloperidol, psychotherapy, and hypnotherapy were used with each having an important role in the apparent cure. It is the feeling that at least in this case, the mother - son relationship is most critical in the development of the syndrome, and that no organic neurological component is present, as has been suggested by several authors. The conclusions would seem to be in accord with the more recent papers relating to this condition. 6 references. (Journal abstract modified)

115045 Chase, Thomas N.; Watanabe, August M. NIMH, 9000 Rockville Pike, Bethesda, MD 20014 Methyldopahydrazine as an adjunct to L-dopa therapy in parkinsonism. ***Neurology.*** **22(4):384-392, 1972.**

A single-blind crossover study was conducted in 14 parkinsonian patients to compare the efficacy and toxicity of L-dopa alone and in combination with alpha-methyldopahydrazine, an extracerebral inhibitor of amino acid decarboxylase. Concomitant administration of decarboxylase inhibitor reduced the optimal therapeutic dose of L-dopa by 76%. Overall neurologic improvement averaged 63% with L-dopa alone and 65% when combined with methyldopahydrazine. Combined therapy substantially decreased the incidence of L-dopa induced emesis, thus permitting a marked acceleration in the rate at which the dose of L-dopa could be increased to therapeutic levels. The frequency of other common side effects of L-dopa such as hypotension and the induction of new adventitious movements were not significantly altered by methyldopahydrazine. No toxic effects attributable to the decarboxylase inhibitor, given alone or together with L-dopa, were observed in the parkinsonian patients or in an additional group of 17 neurologic patients. 30 references. (Author abstract)

115198 Simpson, G.M.; Beckles, D.; Isalski, Z.; Lee, J.H. Early Clinical Drug Evaluation Unit, Rockland State Hospital, Orangeburg, NY Some methodological considerations in the evaluation of drug-induced extrapyramidal disorders: a study of EX10-029, a new morphanthridine derivative. ***Journal of Clinical Pharmacology and New Drugs.*** **12(4):142-152, 1972.**

An evaluation of a new, potential anti-parkinson compound (EX10-029) was made. EX10-029 had a beneficial effect on drug induced extrapyramidal symptoms, although the demonstration of this effect was not as unequivocal as might have been desired. Both Neurological Scale scores and handwriting changed in the expected direction, although the size of change did not necessarily reach statistical significance. Changes in the psychiatric condition of the patients were unrelated to any obvious intervention and were therefore considered to be random. There was no evidence of a stimulating or symptom exacerbating effect with EX10-029, although this may have been obscured by the neuroleptics the patients were receiving. There was a tendency for blood pressures and pulse rates to increase during the experimental phase of the study, although the magnitude of change was small. Occasional abnormal laboratory findings were noted but did not appear to be drug related. 16 references. (Author abstract modified)

115282 Fisher, E.; Spatz, H.; Heller, B.; Reggiani, H. Laboratorio de Psicofarmacologia y Neuropsiquiatria Experimental, Hospital Nacional J.T.Borda, Buenos Aires, Argentina Phenethylamine content of human urine and rat brain, its alterations in pathological conditions and after drug administration. ***Experientia (Basel).*** **28(3):307-308, 1972.**

Pathological conditions and drug administration are found to alter the phenethylamine content of human urine and rat brain. Phenethylamine excretion is significantly diminished in endogenous depressions. In secondary and atypical depressive states, as well as in arteriosclerotic dementia, normal values were obtained. Abnormally high amounts were found in mania and schizophrenia. During the treatment of endogenous depression with tricyclic dibenzepinic drugs, a normalization of phenethylamine elimination took place. In a circular case of manic-depressive psychosis, a sudden elevation was observed as the state changed from depressive to manic phase. The phenethylamine content of rat brain is signifi-

cantly elevated by iproniazide, imipramine, and chlorimipramine, and reduced by reserpine. Further investigations are being conducted to determine the mechanism by which tricyclic dibenzepinic drugs elevate phenethylamine concentrations. 8 references.

116384 Tanka, Hiromitsu; Takayama, Iwao; Kawano, Michio; Ohkubo, Naoyoshi; Yoshimuta, Sunao; Kono, Yasuko; Hayashi, Yachiyo; Tominaga, Koichi. Kagoshima University, Japan Clinical studies on the evaluation of the effect of medazepam. *Journal of Japanese Psychosomatic Society (Fukuoka).* 12(1):59-64, 1972.

Using the double-blind crossover method, the effect of medazepam on neuroses and psychosomatic diseases was compared with that of diazepam and a placebo in 40 neurotics and 45 psychosomatic patients. The results show that medazepam was more effective than the placebo or diazepam for neurotic patients with symptoms of lassitude, anxiety and tension, difficulty in attention, gastrointestinal disturbance, constipation and bodily symptoms of tension. The medazepam was more effective in psychosomatic patients with symptoms of psychic tension and bodily symptoms often seen in the aged such as insomnia, and fear and anxiety. 7 references. (Author abstract modified)

116704 Villeneuve, A. Research Division, Hopital St.Michel-Archange, Quebec 5, Canada The rabbit syndrome: a peculiar extrapyramidal reaction. *Canadian Psychiatric Association Journal (Ottawa).* 17(Special Supplement 2):69-72, 1972.

A panel discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which five cases of an unusual extrapyramidal reaction labeled rabbit syndrome were presented. As in the case of the oral permanent-like dyskinesias, these rabbit-like movements can be intensified by asking patients to follow a labyrinth pattern with a pencil and are also augmented by anxiety and fatigue. However, contrary to the former type of oral dyskinesias, where various degrees of improvement can be obtained with reserpine but more so with alpha-methyldopa, the latter type appears to respond to the administration of antiparkinsonian agents. Therefore, this differential response suggests a different underlying biochemical mechanism, most likely a differential imbalance in the neurotransmitters involved in the normal functioning of the extrapyramidal system. Subtle brain lesions may also be implied in both types of dyskinetic phenomena, as is indicated by the presence of release reflexes which are considered by some to be a sign of brain damage. Moreover, the relationship between nervous structures and brain amines involved in these conditions still remains unclear. In Parkinson's disease a deficiency in the dopamine level of the striatum is assumed to play an important role, and many clinical studies using L-DOPA in the treatment of this disorder are under way. Yet the administration of L-DOPA induces neurological side effects in cases resembling the dyskinesias of the permanent type, in particular of the bucco - linguo - mandibular type. At the present moment no causal relationship can be established with any particular neuroleptic, but some link can be suspected to exist with the more potent ones such as the piperazine phenothiazine derivates. 23 references. (Author abstract modified)

116890 Yaryura-Tobias, J.A.; Diamond, B.; Merlis, S. no address Psychiatric manifestations of levodopa. *Canadian Psychiatric Association Journal (Ottawa).* 17(Special Supplement 2):123-128, 1972.

A panel discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which the clinical action of levodopa (L-Dopa) on a psychotic population is described. Ss were suffering from schizophrenia or alcoholic psychosis. Administration of the drug to schizophrenics resulted in psychiatric and behavioral changes and varied from depression to happiness, increased activity, optimism and alertness. As a group, the physiological reactions were similar to those for stimulant drugs, particularly amphetamine. An increase in sexual interest was also noted, along with perceptual changes, mainly auditory and visual hallucinations. Some explanations for the incidence of psychiatric symptoms during L-Dopa therapy are offered, and it is suggested that reactions may be similar to those suggested by biochemical theories of schizophrenia related to catecholamine metabolism. Reactions among the alcoholic Ss varied and in some cases were similar to those for the schizophrenics. 22 references.

116897 MacDonald, D.J. Psychiatry Department, University of Toronto, Toronto, Ontario, Canada Psychotic reactions during organ transplantation.

***Canadian Psychiatric Association Journal (Ottawa).* 17(Special Supplement 2):15-17, 1972.**

A panel discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which psychotic reactions during organ transplantation are reviewed. Specifically, some observations of reactions occurring during dialysis and when patients are faced with bilateral nephrectomy and renal transplantation are discussed. For some patients reactions include a period characterized by intense uncertainty, fear of death or permanent disability. Sexual impotence or frigidity is almost always present in cases of married patients. Financial insecurity and geographic dislocation frequently complicates the reaction, and confusional or subacute delirious states are common and closely related to electrolyte shifts, fluid balance disorders or toxemia secondary to uric acid retention, hyperpyrexia, infection and anemia. Chemotherapeutic agents are often used in depression occurring during long-term dialysis, and most physicians rely solely upon the imipramine derivatives as antidepressants. In cases of bilateral nephrectomies to facilitate control of hypertension and to remove a potential source of tissue-bound antibodies during long-term dialysis, the common reaction is severe alarm bordering on panic. Reactions following transplantation procedures are likewise frequently dramatic, involving short-term elation in mood, often followed by manic episodes or profound depressive psychosis.

117599 Chien, Ching-piao; Keegan, David. Boston State Hospital, Boston, MA Diazepam as an oral long-term anticonvulsant for epileptic mental patients. *Diseases of the Nervous System.* 33(2):100-104, 1972.

Forty two mental patients at the Boston State Hospital with past histories of repeated grand mal seizures and of being on long-term anticonvulsants, were placed on a six month study comparing diazepam with previous anticonvulsant medications. The patients were randomly distributed into two groups: the standard treatment group (STD) remained on its previous anticonvulsant medication (diphenylhydantoin and phenobarbital) and the other group was changed from standard anticonvulsants to diazepam. Out of 22 patients in the STD, eight patients experienced seizures compared to the seven out of 20 patients who were placed on diazepam. The total number of seizures and days required for onset of seizures during the study were almost identical in both groups and it would appear superficially, at least from these measures that sole usage oral diazepam is as effective as standard anticonvulsant agents in the control of seizures. However, if the severity of seizures were analyzed, then the diazepam group had a significantly higher incidence of grand mal seizures, while the STD experienced more minor seizures. Mental status measures by NOSIE indicated that patients on diphenylhydantoin and phenobarbital showed better control in behavior, especially the psychotic symptoms, than the patients on diazepam. 20 references. (Author abstract)

118552 Greenhill, Laurence L.; Rieder, Ronald O.; Wender, Paul H. Laboratory of Psychology, Bldg.10, Room 2N222, NIMH, Bethesda, MD 20014 Lithium in the treatment of hyperactive children. (Unpublished paper). Bethesda, MD, NIMH, 1972, 19 p.

Nine hyperactive children unresponsive to safe doses of stimulants or tranquilizers were placed on a trial of lithium carbonate. Three children with some affective symptomatology responded briefly to lithium, but became tolerant within one to three months. The later addition of normal doeses of dextroamphetamine to the lithium regime brought back a second temporary behavioral improvement in both of the children tried, children who had initially responded to lithium. Amphetamines alone worsened hyperactive behavior in these three lithium responders. Five other children did poorly on lithium, but showed mild to moderate improvement on dextroamphetamine. All children were maintained safely on lithium for three to nine months, with rare mild toxic reactions and one case of slightly elevated thyroid values. Side effects responded to dosage reduction. It is concluded that lithium is as safe a drug for the child psychiatric population as it is for adults, but has limited applications for the hyperactive syndrome of childhood. 10 references. (Author abstract)

12 PSYCHOTOMIMETIC EVALUATION STUDIES

113265 Ferlemann, Mimi. author address not given LSD: miracle or menace? *Menninger Perspective.* 3(2):11-15, 1972.

Lysergic acid diethylamide (LSD) has been employed as a tool in the treatment of some psychiatric disorders, with psycholytic therapy and psychedelic - peak therapy being the 2 major approaches. In psycholytic therapy, the aim is to uncover the unconscious material which can be analyzed psychodynamically during LSD therapy and during subsequent psychotherapy sessions. This type of therapy is long -term with multiple sessions and low doses of LSD. In psychedelic - peak therapy, a larger dose of LSD is administered, and one of the immediate aims is achievement of a peak or transcendental experience. Psychotherapy can be important both before and after the session to help the subject to integrate whatever insight has been experienced. Thus far, patients who have received LSD therapy have usually been individuals with whom traditional treatment has failed.

115713 Bailey, K.; Verner, D. Research Laboratories, Food and Drug Directorate, Ottawa K1A OL2, Canada Correlation between potency and UV spectra of hallucinogenic amphetamines. *Journal of Pharmaceutical Sciences.* 61(3):480-481, 1972.

A study to correlate potency and ultraviolet (UV) spectra of hallucinogenic amphetamines was made. Eight methoxylated amphetamine hydrochlorides were investigated to determine the relationship between UV absorption maximum and potency and between the molar absorptivity and potency. Results support previous evidence that the ease of perturbability of gamma electrons (in the highest occupied molecular orbital) allows the formation of a low energy, reversible, gamma molecular complex with a brain receptor. 8 references.

13 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

107116 Carpenter, W.T.; Strauss, J.S.; Bunney, W.E. Clinical Research Unit, Adult Psychiatry Branch, NIMH, Bethesda, Md. 20014 The psychobiology of cortisol metabolism: clinical and theoretical implications. (Unpublished paper). Rockville, Md.NIMH, 1972, 32 p.

The role of cortisol in enhancement of gluconeogenesis, fat metabolism, water and mineral metabolism, the cardiovascular system, the striated muscle system, and hematologic processes is briefly examined. Behavioral observations relating to patients with cortisol abnormalities are reviewed. Excess and deficiency of cortisol are shown to be related to both depression and euphoria, to personality changes, and to schizophrenic like reactions. The relationship of cortisol to sleep and perception is also examined. Theoretical implications of cortisol activity to brain function are considered. Hypotheses pertaining to metabolic effects on minerals, catecholamines, indoleamines, and adenosine 3,5-monophosphate are examined. Since psychiatrists are seldom consulted in cases of adrenal insufficiency, methods of assessing and treating emotional problems related to hypocortisolism and hypercortisolism are suggested. 86 references.

107450 Fann, William E.; Davis, John M.; Janowsky, David S.; Cavanaugh, John H.; Kaufmann, John S.; Griffith, John D.; Oates, John A. Dept.of Pharmacology, Vanderbilt Univ., Nashville, Tenn. Effects of lithium on adrenergic function in man. *Clinical Pharmacology and Therapeutics.* 13(1):71-77, 1972.

The effects of lithium on adrenergic function in man was investigated. The blood pressure response to infused norepinephrine (NE) and tyramine was investigated in 8 hypomanic patients who were studied during a control period and after 7 to 10 days of lithium treatment. Lithium decreased the pressor effect produced by NE, failed to alter the pressor effect to infused tyramine, failed to alter platelet serotonin content, and decreased the pressor response to infused NE in man. 44 references. (Author abstract modified)

107453 Sellers, Edward M.; Carr, Gordon; Bernstein, Jerrold G.; Sellers, Sirje; Koch-Weser, Jan. Clinical Pharmacology Unit, Dept.of Medicine and Pharmacology, Massachusetts General Hospital, Boston, Mass. Interaction of chloral hydrate and ethanol in man: II.Hemodynamics and performance. *Clinical Pharmacology and Therapeutics.* 13(1):50-58, 1972.

Changes in heart rate, arterial pressure, and skin temperature and in performance tests were studied in 5 male volunteers after ingestion of placebo, ethanol, chloral hydrate, both drugs, or ethanol after 7 days of chloral hydrate pretreatment. Ethanol ingestion was always associated with an increase in heart rate at 0.5and 1.0hours; this tachycardia was enhanced by pretreatment with chloral hydrate. Chloral hydrate followed by ethanol also caused greater increases in skin tem-

peratures than other treatments. At the peak of the reaction the blood acetaldehyde level was only half that after ethanol alone which had caused no reaction. The ability to perform a complex motor task was poorest when chloral hydrate was taken with ethanol. Auditory vigilance was significantly impaired by ethanol; concurrent chloral hydrate treatment further decreased performance. The knock-out drop effect was not seen. 16 references. (Author abstract modified)

107454 Sellers, Edward M.; Lang, Mary; Koch-Weser, Jan; LeBlanc, Eugene; Kalant, Harold. Clinical Pharmacology Unit, Dept.of Medicine and Pharmacology, Massachusetts General Hospital, Boston, Mass. Interaction of chloral hydrate and ethanol in man: I.Metabolism. ***Clinical Pharmacology and Therapeutics.*** **13(1):37-49, 1972.**

The interaction of chloral hydrate and ethanol metabolism was studied in 5 normal male volunteers. Compared to chloral hydrate alone, ingestion of ethanol 30 minutes after chloral hydrate results in significantly higher and more prolonged concentrations of plasma trichloroethanol and in lower plasma trichloroacetic acid levels and urinary trichloroethanol glucuronide. Chloral hydrate ingestion in turn affects ethanol metabolism and causes peak blood ethanol concentrations to be reached earlier and to be higher than after ethanol alone. Accompanying the higher blood ethanol levels are lower blood acetaldehyde concentrations. Blood ethanol concentration 1/2 hour after ethanol ingestion is linearly related to the plasma trichloroethanol level at the time of ethanol ingestion. In vitro studies showed that the elevated blood ethanol concentrations are due to competitive inhibition of alcohol dehydrogenase by trichloroethanol. Ethanol stimulates NADH production and thereby increases the rate of chloral hydrate reduction to trichloroethanol by liver alcohol dehydrogenase. Human red blood cells also reduce chloral hydrate to trichloroethanol. 38 references. (Author abstract modified)

107586 Kabins, Sherwin A. Council on Drugs, American Medical Association, 535 N.Dearborn St., Chicago, Ill. 60610 Interactions among antibiotics and other drugs. ***Journal of the American Medical Association.*** **219(2):206-212, 1972.**

Since it is impossible in the absence of adequate in vitro studies to predict whether a combination of antibiotics will be synergic, additive, indifferent, or antagonistic, a number of interactions and the mechanism of these interactions involving antimicrobial agents and other drugs in man are reviewed. Furazolidone, partly because of its inhibition of monoamine oxidase, interacts with a number of drugs such as amphetamine, barbiturates, chloral hydrate, phenothiazines and tricyclic antidepressants. Findings are provided in tables which summarize: (1) infections favorably affected by antibiotic combinations, (2) mechanisms of antimicrobial synergy, and (3) guidelines to synergistic and antagonistic combinations. 18 references.

107589 no author. author address not given Alcohol-induced sensitivity and tolerance. ***Journal of the American Medical Association.*** **219(4):508-509, 1972.**

Recent studies at the cellular and subcellular levels on alcohol induced sensitivity and tolerance to sedatives suggest that enzyme activity plays a significant part in the mechanism. Studies on pentobarbital and meprobomate metabolism in inebriated rats and human volunteers have indicated that the basic mechanism of drug sensitivity in acute alcoholism is enzyme inhibition in the liver rather than drug synergism or summation of drug effects on the brain. Similarly, alcohol was found to resemble phenobarbital, which interacts with hepatic microsomes, as an enzyme inducing drug. Hence enhancement of drug metabolizing as well as of alohol oxidizing enzymes is apparently a significant factor in the increased tolerance of chronic alcoholics to sedatives. 3 references.

108610 Zsoter, Thomas T.; Gospodarowitz, Maria. Division of Clinical Pharmacology, Toronto Western Hospital, University of Toronto, Toronto, Canada The effect of diazepam and pentazocine on the venomotor reflexes in man. ***Journal of Clinical Pharmacology and New Drugs.*** **12(2-3):89-94, 1972.**

The effect of diazepam and pentazocine on venomotor reflexes was studied. Diazepam (10 or 6mg intravenously in 15 volunteers) decreased blood flow and venous tone in the forearm. Venoconstriction caused by Valsalva maneuver was markedly diminished after the drug. Venomotor reflexes activated by deep inspiration or hyperventilation were also depressed, but less consistently. Pentazocine (0.75mg/kg intravenously in 15 other volunteers) had no significant effect on forearm venous tone. Venoconstriction induced by Valsalva maneuver became

less pronounced after the drug was given, but changes in heart rate were not altered. Venomotor reflexes may be affected by drugs that have no effect on the peripheral autonomic nervous system but that act on the central nervous system. 24 references. (Author abstract modified)

108966 Gibson, P.F.; Wright, N. Department of Clinical Chemistry, The Royal Infirmary, Edinburgh, EH3 9YW, Scotland Ethchlorvynol in biological fluids: specificity of assay methods. ***Journal of Pharmaceutical Sciences.*** **61(2):169-171, 1972.**

Acute overdosage with the hypnotic sedative ethchlorvynol (5-chloro-3-ethylpent-1-en-4-yn-3-ol) leads to respiratory depression and hypotension with prolonged deep coma and its associated complications. The concentrations of ethchlorvynol in blood, urine, and hemodialysate from a patient with acute ethchlorvynol overdosage were determined by chemical methods and gas - liquid chromotography (GLC). In comparison, the colorimetric and spectrophotometric methods were shown to be nonspecific, apparently measuring metabolites as well as unchanged drug. GLC provides a specific method for the quantititative estimation of ethchlorvynol in biological fluids. It was used to show that, while the drug can be effectively removed from the body by hemodialysis, the urinary excretion of unchanged drug is negligible. 27 references. (Author abstract modified)

110986 Hollister, Leo E. Veterans Administration Hospital, 3801 Miranda Ave., Palo Alto, Cal. 94304 Drug therapy: mental disorders --antipsychotic and antimanic drugs. ***New England Journal of Medicine.*** **286(18):984-987, 1972.**

An overview of drug therapy in mental disorders is presented. Types and choice of antipsychotic drugs, general principles in their use, side effects and complications, combinations and interactions are discussed. Antimanic drugs, indications for lithium carbonate, toxicity, and pharmacokinetics are also discussed. 10 references.

111219 Barrass, B.C.; Coult, D.B. Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, England Interaction of some centrally active drugs with caeruloplasmin. ***Biochemical Pharmacology (Oxford).*** **21(5):677-685, 1972.**

Centrally active drugs such as d-lysergic acid diethylamide (LSD), and to a lesser extent ibogaine and 2-bromo-LSD inhibited the caeruloplasmin catalysed oxidation of 5-hydroxytryptamine but accelerated the oxidation of noradrenaline and dopamine. Harmine and harmol inhibited the enzymic oxidation of all 3 substrates. Centrally active anticholinergics and substituted phenylethylamines did not affect the enzymic oxidation of these substrates. Some drugs used in the treatment of mental illness affect the caeruloplasmin catalysed oxidation of noradrenaline, dopamine, and 5-hydroxytryptamine. Tranquillizers of the phenothiazine class, for example, accelerated the oxidation of all 3 substrates while antidepressant drugs (other than monoamine oxidase inhibitors) inhibited the oxidation of all 3 substrates. Caeruloplasmin cannot be generally used as a model for those receptors with which some centrally active drugs must interact to produce their characteristic effects; however, caeruloplasmin, or an enzyme with similar properties, may be of importance in controlling the relative concentrations of noradrenaline, dopamine, and 5-hydroxytryptamine in those areas of the brain where these compounds act as neurotransmitters. 21 references. (Author abstract)

111323 Savage, Charles; McCabe, O.Lee. University of Maryland School of Medicine, College Park, Maryland Psychedelic (LSD) therapy of drug addiction. ***In: Brown, C., The drug abuse controversy.*** **Baltimore, National Educational Consultants, 1972. 270 p. (p.145-163).**

As part of a symposium on the controversy surrounding drug addiction, psychedelic (LSD) therapy of drug addiction is discussed. Methodology of the treatment is outlined along with a historical survey of its existence and use. An interim report is then offered of a research project designed to assess the therapeutic impact of psychedelic therapy in what is thought to be its optimal form. Preliminary results indicate that the therapy as conducted and in combination with a brief period of residence in a therapeutic community offers potential for being a safe, short-term method of rehabilitating the chronic, hard-core heroin addict.

111553 Akpinar, S.; Itil, T.M.; Holden, J.M.C.; Hsu, W. Missouri Institute of Psychiatry, 5400 Arsenal St., St.Louis, Mo. 63139 Qualitative and quantitative EEG changes of intramuscular thiothixene and trifluoperazine in chronic schizophrenia. ***Diseases of the Nervous System.*** **33(1):40-45, 1972.**

Qualitative and quantitative EEG changes of parenteral trifluoperazine and thiothixene were studied in a group of chronic schizophrenic patients using a double-blind crossover study design. It was found that both compounds produce EEG profiles which are typical for major tranquilizers. The major difference between the 2 compounds was the increase of high frequency fast activity after thiothixene. The hypothesis was made that major tranquilizers have not only a central inhibitory but also a central stimulatory effect. The resulting clinical effects depend upon not only the types of patients involved, but also the single and total daily dosages given. 21 references. (Author abstract modified)

111673 Goodwin, Frederick K.; Post, Robert M. Laboratory of Clinical Science, Bethesda, Md. 20014 The use of probenecid in high doses for the estimation of central serotonin turnover in patients: differences in diagnostic groups and the effects of amine precursors and synthesis inhibitors. (Unpublished paper). Rockville, Md.NIMH, 1972, 17 p.

Results of administration of probenecid to patients with affective illness, heroin addicts on methadone, and normal and neurological controls are reported. Findings reported include: levels of 5-hydroxyindoleacetic acid (5-HIAA); relationships of changes in 5-HIAA to dose and duration of probenecid; probenecid induced accumulation of 5-HIAA in different diagnostic groups; and effects of drugs on 5-HIAA accumulation. Suggestive evidence is presented that the 5-HIAA accumulation of probenecid does indirectly reflect serotonin synthesis. 32 references.

112029 Gram, Lars F.; Overo, Kerstin Fredricson. Psychochemistry Institute, University of Copenhagen School of Medicine, Copenhagen, Denmark Drug interaction: inhibitory effect of neuroleptics on metabolism of tricyclic antidepressants in man. *British Medical Journal (London).* 1(5798):463-465, 1972.

Total urinary excretion of radioactivity after oral or intravenous administration of a test dose of 14C-imipramine was measured in 8 patients. They were tested before, during, and after treatment with neuroleptics. Excretion diminished while the patients were being treated with perphenazine, haloperiodol, or chlorpromazine, though not during flupenthixol treatment. Total urinary excretion of radioactivity and plasma levels of metabolites and unchanged drug were measured in 5 patients after a test done of 14C-nortriptyline. Each patient was tested before and again during perphenazine treatment. In all patients perphenazine treatment caused: decrease of total urinary excretion, decreased plasma level of metabolites, and increased plasma level of unchanged nortriptyline. These results indicate that neuroleptics inhibit the metabolism of tricyclic antidepressants in man. 19 references. (Author abstract)

112074 Viau, Jean-Paul; Epps, Joyce E.; Di Carlo, Frederick J. Department of Drug Metabolism, Warner-Lambert Research Institute, Morris Plains, N.J. Prazepam metabolism in vitro. *Biochemical Pharmacology (Oxford).* 21(4):563-569, 1972.

Comparative information on the biotransformation of prazepam in vivo and in vitro is discussed. 14C-prazepam (7-chloro-1-cyclopropylmethyl-5-phenyl-1H-1,4-benzodiazepin-2-one) labeled either in the 5-phenyl ring or in the cyclopropyl sidechain, was incubated with 9000 g supernatant fractions prepared from livers of dogs, untreated and phenobarbital treated rats, and untreated and phenobarbital treated mice. Ring-labeled prazepam was also incubated with liver supernatants from humans. N-dealkylation was the major pathway of prazepam metabolism in vitro. The liver enzymes of all species except untreated mice were able to metabolize prazepam to varying amounts of oxazepam. Pretreatment of rats with phenobarbital resulted in an increase of both desalkylprazepam and oxazepam formation from prazepam. 16 references. (Author abstract modified)

112933 Learoyd, Brian M. North Ryde Psychiatric Centre, North Ryde, Australia The effect of sedatives on the metabolic rate during alcohol withdrawal. *Quarterly Journal of Studies on Alcohol.* 33(1):22-32, 1972.

Although large doses of sedative, hypnotic or tranquilizing drugs are often used to manage the alcohol withdrawal syndrome, it has been suggested that these drugs may, in fact, exert a disinhibiting effect. Commonly used sedatives given to 66 alcoholics in withdrawal caused an increased metabolic rate in 29, a depressed rate in 26 and no effect in 11. The therapeutic implications of these findings are reviewed. 23 references.

112980 Watson, Michael; Gabica, Joe; Benson, W.W. Idaho State Department of Health, Boise, Idaho Serum organochlorine pesticides in mentally retarded patients on differing drug regimens. *Clinical Pharmacology and Therapeutics.* 13(2):186-192, 1972.

Serum concentrations of p,p'DDT and its metabolite p,p'DDE were estimated by electron capture gas chromatography in a group of mentally retarded institutionalized patients receiving antiseizure and tranquilizing chemotherapy. Control patients not taking drugs tended to resemble the general population in terms of organochlorine residues, but drug takers showed greatly lowered levels of both p,p'DDE and p,p'DDT. The combination of phenobarbital and diphenylhydantoin seemed to be the most effective in depressing serum pesticides and remained so even in patients taking other drugs concurrently. P,P'DDE was found at detectable levels in all patients sampled, but the frequency of occurrence of p,p'DDT was considerably decreased among the drug takers. This was particularly true of patients receiving both phenobarbital and diphenylhydantoin concurrently. The possibility that the catabolism of p,p'DDT is induced preferentially to that of p,p'DDE by the phenobarbital - diphenylhydantoin combination is discussed. 15 references. (Author abstract)

113134 Owen, J.R.; Irani, S.F.; Blair, A.W. Department of Paediatrics, Southmead Hospital, Bristol, England Effect of diazepam administered to mothers during labour on temperature regulation of neonate. *Archives of Disease in Childhood (London).* 47(251):107-110, 1972.

Falls in temperature in the first nine hours after delivery were studied in a group of 12 babies whose mothers had received diazepam in labor, and in 13 comparable babies not exposed to diazepam. A significantly lower mean temperature was found in the test group within the first three hours. Cord blood levels of diazepam did not correlate with either maternal levels at delivery, the extent of the temperature drop, or the condition of the baby at birth, though there was an increased incidence of assisted delivery and resuscitation of the infants in the test group. 11 references. (Journal abstract)

113794 Brodie, H.K.H.; Murphy, D.L.; Goodwin, F.K.; Bunney, W.E. National Institute of Mental Health, Rockville, Md. The effects of alphamethylparatyrosine on the sleep of patients with affective disease. *Psychophysiology.* 9(1):90, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep a study is reported in which alphamethylparatyrosine (AMPT), an inhibitor of tyrosine hydroxylase and the rate limiting enzyme in catecholamine synthesis, was administered to 10 patients with affective disease in 250mg capsules 2 to 4 times daily. The dose was gradually increased until a clinical change was noted, unacceptable side-effects encountered, or maximum dosage of 4g/day was achieved. Room checks were made every 30 min during the night to assess the amount of time each patient slept. The administration of AMPT decreased 24 hr urinary excretion of dopamine, 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxphenylglycol to less than 30% of pretreatment levels. Excretion of these metabolites returned to normal pretreatment levels approximately 5 days after AMPT was discontinued. Spinal fluid homovanilic acid levels decreased by more than 40% in each of 3 patients studied. No significant change in total hours of sleep was noted when comparing the 4 day predrug placebo time with the last 4 days on AMPT (period of maximum dosage). However, a significant decrease in total sleep was noted during the first 6 days off drug in comparison with the last 4 days on drug. Dopamine has been shown to be an alerting agent, and a rebound in its synthesis following discontinuation of AMPT may be responsible for the observed decrease in total sleep. However, increased receptor sensitivity may also be involved. (Journal abstract modified)

113795 Dunleavy, D.L.F.; Oswald, Ian. University of Edinburgh, Scotland Depression, mono-amine oxidase inhibitors, and REM sleep. *Psychophysiology.* 9(1):90, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which 18 depressed patients are monitored in the sleep laboratory throughout their stay in hospital. Each patient performed a daily self-rating of mood on a visual analog scale. There was an initial placebo period of 2 to 20 days followed by phenelzine in a daily dosage of 60, 75 or 90mg, this dose remaining constant for each patient. Total suppression of the signs of pardoxical sleep occurred in each case and there was a clear cut close response relationship for this abolition, suppression occur-

ring in 8 days with 75 and 90mg and taking 15 days with 60mg. Delay to sleep onset was reduced and as therapy with phenelzine was continued it was noted that there were more frequent but transient awakenings during the night. Muscle tone was heightened throughout and there was dissociation of the component features of REM sleep for a few nights prior to the total abolition of its signs. Fifteen patients showed significant clinical improvement. The results indicate that the self-rated and clinical improvement were related in time to the total abolition of REM sleep. It is postulated that this change in the EEG is a manifestation of change in basic brain functioning which in turn leads to mood improvement. (Journal abstract modified)

113797 Fisher, Charles; Kahn, Edwin; Edwards, Adele; Davis, David. The Mount Sinai School of Medicine Total suppression of REM sleep with the MAO inhibitor Nardil in a subject with painful nocturnal REMP erection. *Psychophysiology.* 9(1):91, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep a case is reported of a 46 year old male suffering from painful nocturnal REMP errections who was given the monoamine oxidase inhibitor Nardil, 45 to 75mg daily over a period of several months. The findings of the Wyatt and Oswald groups were confirmed: a nearly total suppression of REM sleep for nearly 70 nights was brought about which was followed by a marked REM period rebound. All aspects of REM periods were suppressed except erections which were reduced in number by 25%, with marked reduction in number of awakenings with painful erection. Although the subject had excellent recall of long narrative dreams during baseline, with Nardil suppression there was no evidence that dreaming was occurring. Only brief thought like content or reports of single isolated static visual images could be elicited. The prolonged suppression of REM sleep does not appear to be harmful. One serious side effect occurred, a total loss of sexual desire and interest accompanied by difficulty in getting erection and ejaculation. The psychological process of dreaming can be eliminated without harmful effect. There is no evidence of compensatory NREM Dreaming or other substitute activity. (Journal abstract modified)

113798 Fisher, Charles; Kahn, Edward; Edwards, Adele; Davis, David. The Mount Sinai School of Medicine Effects of Valium on NREM night terrors. *Psychophysiology.* 9(1):91, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is shown that marked reduction in incidence and intensity of stage 4 night terrors in 7 subjects brought about by administering 5 to 20mg Valium nightly. Five subjects showed 38 to 90% (mean 69%) reduction from baseline levels. While on drug all subjects showed either total or nearly total abolition of stage 4 and marked stage 3 reduction. After drug discontinuation, when subjects were either on placebo or no medication, 5 of 6 subjects continued to show reduction in incidence of night terrors for several months to over a year. In 4 instances, reduction was associated with variable degrees of failure of delta sleep to return to baseline levels. One subject returned to night terror baseline levels although there was progressive reduction in stage 4; in another the reverse effect occurred. There were no ill effects from prolonged suppression of night terrors or delta sleep. Only 1 subject showed compensatory displacement phenomena resulting from suppression. As Valium brought about progressive decrease in night terrors from stages 3 and 4, there was temporary displacement to stage 2, then to stage 1 REM, and finally to waking hours in the form of daymares. With continued administration there was marked decrease in intensity of awakenings in all sleep stages. (Journal abstract modified)

113802 Kales, J.D.; Bixler, E.O; Slye, E.I.; Baker, M.; Kales, A. Milton S.Hershey Medical Center, UCLA Sleep Research and Treatment Facility, Los Angeles, California Comparison of subjective reports and EEG findings under conditions of placebo or flurazepam (Dalmane) administration and withdrawal. *Psychophysiology.* 9(1):92, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep results are given of a previously reported study in which 12 insomniac subjects were studied under the conditions of no treatment, placebo administration and administration of flurazepam 30mg. Upon awakening each morning, subjects completed a questionnaire which was a self-evaluation of the previous night's sleep. Two of the 3 groups of subjects underwent

drug administration as well as placebo administration and no treatment conditions. In both groups, the EEG findings indicated a marked decrease in sleep latency, wake time after sleep onset and total wake time with drug administration. The subjective reports in the morning were in agreement with this; the subjects reported a decrease in the time required to fall asleep and an increase in the total hours of sleep. The third group of subjects only underwent placebo and not treatment conditions. The EEG findings indicated no differences between no treatment and placebo conditions for sleep latency, wake time after sleep onset, and total wake time. The subjective reports were again in agreement with the results. These results suggest that there is agreement between changes in EEG findings of sleep induction and sleep maintenance and subjective reports in the morning. (Journal abstract modified)

113803 Allen, C.; Scharf, M.B.; Kales, A. Milton S.Hershey Medical Center, UCLA Sleep Research and Treatment Facility, Los Angeles, California The effect of flurazepam (Dalmane) administration and withdrawal on REM density. *Psychophysiology.* 9(1):92-93, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep a study is reported in which eye movement frequency within REM period (REM density) was separately analyzed. Subjects were administered flurazepam and each REM period was divided into 10 sec epochs and the percentage of total REM epochs per night which contained at least 1 eye movement was determined. The results were as follows: last baseline night, 38% of REM epochs has 1 or more eye movements; first drug, 33%; last drug, 27%; first withdrawal, 33%; fifth withdrawal, 38%; and seventh withdrawal, 36%. These results indicated that drug administration produced a decrease in the density of rapid eye movements which was most pronounced on the last drug night. Following drug withdrawal, REM density values returned only to baseline without any REM rebound. The findings suggest that there is a differential effect of the drug on the phasic phenomenon of REM sleep with a possible reduction in the intensity of this sleep stage. (Journal abstract modified)

113804 Kales, A.; Ritvo, E.R.; Preston, T.A.; Scharf, M.B.; Tan, T.L. Milton S.Hershey Medical Center, UCLA Sleep Research and Treatment Facility, Los Angeles, California Effects of prolonged administration of L-Dopa on the sleep patterns of autistic children. *Psychophysiology.* 9(1):89-90, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are provided in which 3 autistic children were studied in the sleep laboratory in order to determine the possible effects of L-Dopa on sleep. They were monitored (1) for several nights prior to L-Dopa administration, (2) during the first 10 to 14 nights of drug administration, (3) after periods ranging from 2 to 6 months of continuous drug use, and (4) immediately following drug withdrawal. In each interval of the study, subjects were studied for 3 to 15 consecutive laboratory nights. The only striking observation in this study occurred on 3 occasions when the autistic children were being readapted to the sleep laboratory. There was an extremely high percentage and absolute amount of REM sleep on the first readaptation night. This is in marked contrast to the usual finding in the laboratory of a decrease in REM sleep on such readaptation nights. The lack of consistent change in REM sleep during L-Dopa administration in this study is in agreement with previously reported findings of no consistent change in REM sleep during L-Dopa administration in patients with Parkinson's disease. (Journal abstract modified)

113898 Minard, James; Mosser, Robert; Moore, Leslie; Hayhurst, Viola; McElroy, Evelyn. Maryland Psychiatric Research Center Latency of eye movements directly observed after the onset of neonate sleep: a replicated study. *Psychophysiology.* 9(1):98, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that eye movements were directly and reliably observed beneath the lids of 2 groups of 30 unselected nursery infants each. Latency from lid closure to eye movement was not correlated with sex of infant, maternal age, Apgar score, type of anesthetic, feeding period observed or information suggesting the infant was suspect. The different experimenters conducting each study found similar, statistically significant day to day increases in the latency within the first 3 days of life. Average latency was 4.10 min in study 1 and 4.44 in study 2. Longer latencies were obtained by observers

more distant than 12 to 18 in.from infants, but day to day increase was still present. The neonate of a mother on phenothiazine medication during pregnancy showed no observable sleep onset eye movement at 12 hours and appeared in later days to increase in observable eye movement. On neurological exam opisthotonos was detected. This sign is a known side effect of the drug used. The infant's lack of REM was a striking departure from the general rule for this nursery but is consistent with a polygraphic REM study suggesting REM rebound in another neonate of a mother on phenothiazine during pregnancy. (Journal abstract modified)

113940 Gillin, J.Christian; Jacobs, Leonard S.; Fram, David H.; Snyder, Frederick. National Institute of Mental Health, Rockville, Md. The acute effect of glucocorticoid steroid on human sleep. *Psychophysiology.* 9(1):100-101, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep 12 healthy subjects, aged 18 to 22, were given prednisone orally in a blind fashion 6 hours before bedtime. Six subjects received 5mg, 6 subjects 60mg and 3 subjects were tested a second time at a dosage level of 20mg. There appeared to be a dose related reduction in REM sleep and increase in NREM sleep on the nights of drug administration. At the highest dose tested, these changes were statistically significant, as was an increase in REM latency. (Journal abstract modified)

114561 Post, Robert M.; Gillin, J.Christian; Wyatt, Richard J.; Goodwin, Frederick K.; Snyder, Frederick; Bunney, William E., Jr. National Institute of Mental Health, Rockville, Md. REM sleep suppressing effects of intravenous L-Dopa given during sleep. *Psychophysiology.* 9(1):88, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which 10 depressed patients were given infusions of L-Dopa and a pH matched placebo during undisturbed REM and NREM sleep. Patients were EEG monitored for 139 nights, and slept with a forearm intracatheter attached to a 10 ft polyethelene tube kept open with a dilute heparin - saline solution. Pretreatment with a peripheral decarboxylase inhibitor, MK485-6, potentiated central and minimized peripheral effects of L-Dopa. Infusions of 25 to 30mg of L-Dopa during NREM sleep increased the REM latency to 71.4min compared with 44.3min for placebo. Given at the onset of the first REM period, L-Dopa shortened the REM period to 8.3min compared with 17.4, min for placebo. Five patients received infusions at the onset of the second REM period with placebo (38 min). Total REM and NREM sleep did not differ on L-Dopa compared with placebo infusion nights. Brief awakenings related to infusions occurred in only 16% of infusions. If these infusions are exclused, Dopa's effect on shortening the first REM period maintains its significance. Thus, intravenous L-Dopa appears to both delay the onset and inhibit the maintenance of REM sleep. (Journal abstract modified)

114563 Schmidt, Helmut S.; Knopp, Walter. College of Medicine, Ohio State University, Columbus, OH Sleep in Parkinson's disease: the effect of L-Dopa. *Psychophysiology.* 9(1):88-89, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep experiments are reported in which 2 male patients suffering from Parkinson's disease were studied for 3 months with the first 2 months in a double-blind design. In addition to the daily 16 capsules containing varying amounts of L-Dopa or placebo, patient 1 (65 years) received 20mg and patient 2 (53 years) 40mg diazepam. Sleep recordings were obtained for 2 consecutive nights in the first week, then every Friday night for 11 weeks. The baseline and placebo sleep profile of patient 1 was considerably more normal (less stage 1 without REM, normal stage REM) and much more responsive to L-Dopa (rapid increase of REM sleep percentage as L-Dopa was increased). Disturbed sleep and nightmares occurred when stage REM exceeded 40% at the maximum dose of 5gm L-Dopa per day. Patient 2's response to L-Dopa was a sluggish increase in REM sleep and not exceeding 20% even on 5gm of L-Dopa per day. Noteworthy for both patients is the complete absence of stages 3 and 4 (perhaps due to diazepam) and a mean number of body movements of less than 2 per night. It is concluded that L-Dopa doses indeed increase REM sleep, and that a Parkinsonian patient's sleep profile is a sensitive barometer of his responsivity to L-Dopa and a useful guide as to the rate of increase and the minimum effective dose of L-Dopa. (Journal abstract modified)

114567 Fram, David H.; Gillin, J.Christian; Wyatt, Richard J.; Snyder, Frederick. National Institute of Mental Health, Rockville, Md. The waking action of histidine: evidence to the contrary. *Psychophysiology.* 9(1):85, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that histamine has been implicated as a possible waking factor in a number of studies. To investigate this further, L-histidine, the amino acid precursor of histamine, was administered to 3 patients with narcolepsy in doses up to 20g/day for up to 2 weeks, and serial nightly records and periodic all day records of EEG, EOG and EMG were obtained. These records were compared with ones taken under identical conditions while subjects were taking placebo both before and after histidine administration. A questionnaire to assess sleep and waking variables, subjectively was also completed twice daily by subjects during drug and placebo periods. No difference between drug and placebo periods was found for any sleep variables, including amount of nighttime waking, amount of daytime sleep, amount of REM sleep or amount of delta (stages 3 and 4) sleep. Likewise, no differences were found when the subjective self-assessment ratings were compared. This study does not validate the hypothesis that histamine is a waking factor. It is possible that this inferred action of histamine was masked by the action of histidine itself or the action of other metabolites of histidine also formed when histidine was administered. (Journal abstract modified)

114571 Spitzer, Helga; Zarcone, Vincent; Barchas, Jack; Ryan, Roger; Smythe, Harvey; Dement, William. Stanford University Medical Center, Stanford, CA Administration of 5-hydroxytryptophane to a L-dihydroxyphenylamine treated patient with Shy-Drager syndrome. *Psychophysiology.* 9(1):87, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep a case study is reported of a 46 year old Caucasian female who was in good health until 1966, when she developed the syndrome of dystonic bladder, primary orthostatic hypotension, extrapyramidal and pyramidal signs, and sleep disorder -- the Shy-Drager Syndrome. In view of the findings that L-dopa decreases REM sleep time and that d-1-5-hydroxytryptophane (5-HTP) has a REM sleep time enhancing effect, it seemed indicated to give a trial of 5-HTP in combination with L-dopa to see whether the 5-HTP would protect the patient against the L-dopa induced increase and REM time and the psychotic symptoms. REM time decreased to 0 min when L-dopa was increased to 6g/day. REM time increased to an average of 67 min when L-dopa was discontinued and 5-HTP increased to 1.5g/day. Auditory hallucinations stopped after 3 nights of increased REM time. It should be noted that while L-dopa increased cerebrospinal fluid homovanillic acid to as high as 395ng/ml, the 5-HTP increased 5-hydroxyindoleacetic acid to a maximum of only 57ng/ml. (Journal abstract modified)

114904 Royds, R.B.; Coltart, D.J.; Lockhart, J.D.F. Division of Clinical Pharmacology and Cardiac Dept., St. Bartholomew's Hospital, London, England Pharmacologic studies of indoramin in man. *Clinical Pharmacology and Therapeutics.* 13(3):380-392, 1972.

The effects of indoramin, a new hypotensive drug with competitive alpha-adrenergic receptor blocking properties, were studied in a double-blind investigation in healthy human subjects. Indoramin (20mg.)orally produced a significant fall in blood pressure at high exercise loads when compared with placebo. Indoramin (20 and 40mg.)reduced erect blood pressures during a period of 6 hours when compared with placebo in another double-blind study. Histamine skin wheals were also reduced in a dose related manner but no effect on critical flicker frequency was demonstrated. The pressor response to intravenous norepinephrine showed a parallel time related shift to the right after the intravenous administration of 20mg.of indoramin. The effect of intravenous indoramin (10mg.)on myocardial function was studied with noninvasive techniques. No effect was demonstrated on systolic time intervals, cardiac output, or ejection fraction. Indoramin (20mg.)given orally twice daily for 2 weeks reduced erect and supine blood pressures without evidence of drug accumulation. No drug related effects on biochemical or hematologic values were detected. 24 references. (Author abstract)

114905 Johnson, Philip C.; Cressman, William A.; Driscoll, Theda B. Dept.of Medicine, Baylor College of Medicine, Houston, TX Absorption and excretion of a monoureide hypnotic, capuride. *Clinical Pharmacology and Therapeutics.* 13(3):377-379, 1972.

The absorption and excretion of capuride, a monoureide with a duration of hypnotic effect similar to that of the short acting barbiturates, was examined in humans. The absorption and excretion of 100, 200, 400, and 800mg.doses of capuride-4,5-3H were studied by use of a complete crossover design. The drug was rapidly and completely absorbed. Plasma levels of radioactivity wer e directly proportional to the dose administered. Plasma levels and the 0 to 48 hour cumulative urinary excretion showed a linear correlation to total body weight and to each other. Chronic administration of 400 mg.capuride daily was not found to affect its metabolism. 9 references . (Author abstract modified)

114906 Bieger, Robert; de Jonge, Hendrik; Loeliger, Emil A. Haematology Division, Dept.of Internal Medicine, Leiden Univ. Hospital, Leiden, The Netherlands Influence of nitrazepam on oral anticoagulation with phenprocoumon. ***Clinical Pharmacology and Therapeutics.*** **13(3):361-365, 1972.**

A double-blind trial was carried out on 22 volunteer patients to observe the influence of nitrazepam on the course of long-term anticoagulant therapy with phenprocoumon. Dosage of phenprocoumon remained unchanged for all patients during the eight week trial. Nitrazepam or placebo, assigned at random, was taken every night for a two week period; a subsequent two week period without test drugs was followed by a second series with the other tablet. The last two weeks of the trial were without test drugs. There was no difference between the effects of the placebo and the nitrazepam on the hypocoagulability due to the oral anticoagulant therapy. It is concluded that nitrazepam can safely be prescribed as a hypnotic for patients on long-term anticoagulant therapy. 20 references. (Author abstract)

114909 Reid, John L.; Calne, Donald B.; George, Charles F.; Vakil, Sarosh D. Dept.of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, England Levodopa and pressor amine sensitivity in parkinsonism. ***Clinical Pharmacology and Therapeutics.*** **13(3):400-406, 1972.**

The pressor response to intravenous tyramine and norepinephrine in nine parkinsonian patients on maximally tolerated doses of levodopa was compared to that before treatment. The study was repeated in five patients taking levodopa with L-alpha methyldopahydrazine, a decarboxylase inhibitor which does not cross the blood-brain barrier. There was no significant change in pressor sensitivity to tyramine or norepinephrine on levodopa with or without extracerebral decarboxylase inhibition. It is concluded that chronic levodopa administration does not influence tyramine releasable stores of norepinephrine or adrenergic receptor sensitivity. 29 references. (Author abstract)

115307 Jones, A.B.BeVan; Pare, C.M.B.; Nicholson, W.J.; Price, Kathleen; Stacey, R.S. Department of Psychological Medicine, St.Bartholomew's Hospital, London EC1A 7BE, England Brain amine concentrations after monoamine oxidase inhibitor administration. ***British Medical Journal (London).*** **1(5791):17-19, 1972.**

The concentrations of 5-hydroxytryptamine (5-HT), noradrenaline, and dopamine were estimated post mortem in brain stem, hypothalamus, and caudate nucleus in 33 patients who had been treated with isocarboxazid, clorgyline, or tranylcypromine and 11 controls. Similar and highly significant increases in 5-HT and noradrenaline concentration occurred with all three drugs. The distribution was unimodal, but about a quarter of the patients showed only a small increase in brain amines. Tranylcypromine seemed to have a significantly greater effect on dopamine in caudate nucleus and hypothalamus compared with isocarboxazid and clorgyline. In the doses used chlorpromazine did not reduce the amine concentrations. Four patients with Parkinson's syndrome had low concentrations of dopamine in caudate nucleus in spite of monoamine oxidase inhibitor administration. 17 references. (Author abstract)

115699 Berman, Leon E.A. 6440 Hills Drive, Birmingham, MI 48010 The role of amphetamine in a case of hysteria. ***Journal of the American Psychoanalytic Association.*** **20(2):325-340, 1972.**

The symbolic meaning of amphetamine diet pills and the role they played in the symptom complex of a young woman suffering from hysterical neurosis is discussed. In this case study, the amphetamine symbolically expresses both the phallic and oral elements of her neurosis, representing her illusory penis and her defense against feelings of genital damage. It also represented emergency food supplies and defended against feelings of oral abandonment. In providing a sense of phallic wholeness to reassure her against the illusion of gentital defect, the

amphetamine functioned as a fetish, and as an emergency narcissistic supply to relieve her feelings of separation anxiety, it served as a transitional object. The pharmacological effect of the amphetamine helped to regulate her feelings of self-esteem and provide a sense of narcissistic power. The ego state of activation promoted by amphetamine can be traced directly to its pharmacological effects. Its chemical derivation stems from epinephrine and its autonomic action is sympathomimetic. It produces central nervous system stimulation with increased activity in the brainstem resulting in increased alertness, awareness, and attentiveness. There is evidence to suggest that it also increases the libidinal drive. The psychophysiological state produced by amphetamine, is, therefore, similar to the naturally occurring adrenergic response to stress, sexual excitement, and aggression. 21 references. (Author abstract modified)

115947 Olsen, George D. University of Oregon Medical School, Portland, OR 97201 Methadone binding to human plasma albumin. *Science.* 176(4034):525-526, 1972.

The interaction of L-(1-3H) methadone with human plasma albumin was studied by equilibrium dialysis. The percent of methadone bound to albumin was relatively independent of the concentration of methadone, but was dependent on the concentration of albumin, ranging from 8.0to 43.8% bound as the albumin concentration increased from 0.400 gram to 5.00 grams per 100 milliliters of solution. 13 references. (Author abstract)

115962 Boston Collaborative Drug Surveillance Program. 400 Totten Pond Rd., Waltham, MA 02154 A clinical evaluation of flurazepam. *Journal of Clinical Pharmacology and New Drugs.* 12(5,6):217-220, 1972.

A randomized, double blind trial comparing flurazepam, secobarbital, and placebo was carried out within a comprehensive drug surveillance program, prior to the marketing of flurazepam. The efficacy ratings for flurazepam (30mg) and secobarbital (100mg) were similar. Flurazepam was more effective than placebo, particularly when given repeatedly. Side effect rates were similar for the three treatment groups. It is concluded that the newly marketed drug flurazepam can be included as one of the possible drugs which may be used to treat insomnia. 4 references. (Author abstract)

116528 Schnell, Roger G. 4800 Northeast 20th Terrace, Fort Lauderdale, FL 33308 Drug induced dyskinesia treated with intravenous diazepam. *Journal of the Florida Medical Association.* 59(1):22-23, 1972.

Diazepam in doses of 5mg administered intravenously was found to relieve prochlorperazine induced dyskinesia in a 15-year-old girl. Because of the prompt effect, lack of side effects and ease of administration, diazepam may deserve a place in the treatment of drug induced dyskinesias. 8 references. (Author abstract)

116576 Creese, Ian; Iversen, Susan D. Department of Experimental Psychology, Downing Street, Cambridge, England Amphetamine response in rat after dopamine neurone destruction. *Nature New Biology (London).* 238(86):247-248, 1972.

The effect of dopamine neuron destruction following bilateral 6-hydroxydopamine (6-OHDA) lesions of the SN on the responses to amphetamine in the rat is investigated. It seems clear from the results that rats continue to show locomotor stimulation to amphetamine even after very extensive bilateral damage to the nigro-striatal dopaminergic pathway. Furthermore, for at least 19 days after surgery, the locomotor response is considerably enhanced in such animals. The basis of this effect remains obscure. Several possibilities are given. 27 references.

116594 Goodwin, Guy M.; McCloskey, D.Ian; Matthews, Peter B.C. University Laboratory of Physiology, Oxford, OX1 3PT, England Proprioceptive illusions induced by muscle vibration: contribution by muscle spindles to perception? *Science.* 175(4028):1382-1384, 1972.

Proprioceptive illusions induced by muscle vibration was investigated. When vibration of 100 hertz was applied to the tendon of the biceps or the triceps muscle, the subject made a systematic misjudgment of the angle at the elbow. During contraction, the error could be as much as 40 deg. The subject thought that the elbow was in the position that it would have assumed if the vibrated muscle had been stretched. It is suggested that under suitable circumstances spindle afferent discharges can contribute to perception. 11 references. (Author abstract modified)

116678 Chase, Thomas N.; Ng, Larry K.Y.; Watanabe, August M. NIMH, 9000 Rockville Pike, Bldg.36, Bethesda, MD 20014 Parkinson's disease; modification by 5-hydroxytryptophan. *Neurology.* 22(5):479-484, 1972.

The clinical and biochemical effects of L-5-hydroxytryptophan (5-HTP), the immediate precursor of serotonin, given to seven parkinson patients in combination with alpha-methyl-dopahydrazine, an extracerebral inhibitor of amino acid decarboxylase is reported. A significant increase in bradykinesia and rigidity occurred together with an exacerbation of functional disability. There was, however, no consistent change in resting tremor. In cerebrospinal fluid, levels of 5-hyroxyindoleacetic acid, the principal catabolite of serotonin, increased nearly tenfold during drug treatment. Reciprocal effects of L-5-HTP and L-Dopa on parkinsonian rigidity and bradykinesia may both relate to the action of these monoamine precursors on central dopaminergic transmission. 43 references.

116699 Denber, Michel J.A. University of Rochester, River Campus Station, Box 6643, Rochester, NY 14627 Studies on mescaline XXII: subcellular effects of different blocking agents. ***Canadian Psychiatric Association Journal (Ottawa).*** **17(Special Supplement 2):117-121, 1972.**

A panel discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which the subcellular effects of several blocking agents on mescaline induced states in rats are reported. Specifically, chlorpromazine or thioperazine pretreatment before radioactive mescaline in the rat resulted in significant differences in radioisotope uptake into the whole brain and different subcellular fractions when compared to controls. The diethazine - mescaline combination produced a sharp rise in total brain mescaline and a considerable fall in concentration within the myelin and nerve ending particle fractions. There was an important metabolic transformation of mescaline-8-14C between 30 and 60 minutes in the diethazine - mescaline and mescaline - chlorpromazine groups as determined by thin layer chromatography. 12 references. (Author abstract modified)

117101 Beumont, P.J.V.; Harris, G.W.; Carr, P.J.; Friesen, H.G.; Kolakowska, T.; MacKinnon, P.C.B.; Mandelbrote, B.M.; Wiles, D. Groote Schuur Hospital, Capetown, South Africa Some endocrine effects of phenothiazines: a preliminary report. ***Journal of Psychosomatic Research (Oxford).*** **16(4):297-304, 1972.**

Clinical data and the results of hormonal investigations are presented pertaining to a series of 13 female patients who developed galactorrhoea and/or amenorrhoea while receiving treatment with phenothiazines or related drugs (namely Haloperidol). The report is preliminary and incomplete, but the moderately raised plasma levels of prolactin are in keeping with previous reports concerning phenothiazine induced galactorrhoea. In those patients who presented with a menstrual disturbance the plasma levels of luteinizing hormone were generally maintained at a normal level, although the cyclical rise associated with ovulation was suppressed. This is in marked contrast to the situation that pertains in the menstrual disturbance associated with anorexia nervosa where levels are low. It is further of interest that luteinizing hormone levels are not depressed in the presence of raised prolactin levels, as such an association might have been expected if the effect of the drugs were simply a general suppression of the hypothalamic mechanisms involved in the control of the secretion of gonadotrophins. 20 references.

117604 Jones, D.G.; Lenman, J.A.R.; Robertson, M.A.H.; Turnbull, M.J. Dept.of Pharmacology, Univ.of Dundee, Dundee, DD1 4HN, Scotland Effect of amantadine on the urinary excretion of some monoamines and metabolites in normal and parkinsonian subjects. ***British Journal of Pharmacology (London).*** **44(2):386P-387P, 1972.**

The effects of amantadine on the urinary excretion of some of the monoamines and metabolites was examined in normal and in parkinsonian subjects. Urine samples were collected from patients with Parkinson's disease treated with amantadine, from patients treated with L-dopa plus amantadine, from patients receiving L-dopa alone and from healthy volunteers who received the patient dose of amantadine. L-Dopa, alone or in combination with amantadine produced the expected increases in dopamine and 4-hydroxy-3-methoxyphenylacetic acid excretion but also significantly reduced output of 5-hydroxyindole-3-acetic acid. In those patients receiving the drug combination, the excretion of 5-hydroxyindole-3-acetic acid was reduced to preamantadine levels. The finding that L-dopa reduced the excretion of 5-hydroxyindole-3-acetic acid but not that of methylhistamine supports the suggestion that the decrease may not simply be due to competition between amino acids for absorption or for a decarboxylase enzyme. 13 references.

117606 Curry, S.H.; Lader, M.H.; Mould, G.P.; Sakalis, G. Dept.of Psychiatry, Institute of Psychiatry, Univ.of London, London, England Clinical pharmacology of chlorpromazine. *British Journal of Pharmacology (London).* 44(2):370P-371P, 1972.

Ten drug free psychiatric patients were given chlorpromazine in a study of the clinical pharmacology of the drug. Testing was done: on blood samples after drug dosage; on blood pressure and pulse rate, pupil size, sweat gland activity and EEG; salivary secretion, auditory evoked response, simple auditory reaction time and handwriting; and on timed clinical ratings. After an initial rise, plasma concentrations dropped markedly. The drop in concentrations after the first 14 days may reflect induction of drug hydroxylase activity in the liver. The correlations with peripheral measurements show that concentration data are useful during appraisal of marked side effects such as postural hypotension, but further studies are needed to evaluate the usefulness of plasma chlorpromazine estimations in the clinical management of psychiatric patients. 1 reference.

117634 O'Malley, K.; Sawyer, P.R.; Stevenson, I.H.; Turnbull, M.J. Dept.of Pharmacology and Therapeutics, Univ.of Dundee, Dundee, DD1, 4HW, Scotland Effects of tricyclic antidepressants on drug metabolism. *British Journal of Pharmacology (London).* 44(2):372P-373P, 1972.

The effects of tricyclic antidepressants (amitripytyline; chlorimipramine; desmethylimipramine; imipramine; and nortriptyline.)on drug metabolsim was examined in humans (20-30-years-0ld) and in rats. The effects of these agents was compared in humans after long-term and short-term treatments; and their effects on rat liver drug metabolizing enzymes was investigated. In humans there was a tendency towards an increase in the rate of antipyrine metabolism after either period of treatment. These results are supported by the rat data in theat the rate of hexobarbitone metabolism tended to be increased after chronic exposure to the antidepressants. Data indicates that in both man and the rat the antidepressants studied appeared to act as weak inducers of drug metabolism. 4 references.

118799 Harvey, D.J.; Glazener, L.; Stratton, C.; Nowlin, J.; Hill, R.M.; Horning, M.G. Institute for Lipid Research, Baylor College of Medicine, Houston, TX 77025 Detection of a 5-(3,4-dihydroxy-1,5-cyclohexadien-1-yl) metabolite of phenobarbital and mephobarbital in rat, guinea pig and human. *Research Communications in Chemical Pathology and Pharmacology.* 3(3):557-565, 1972.

The metabolism of phenobarbital and mephobarbital was studied in the rat, guinea pig and human using methods based on gas chromatography and gas chromatography - mass spectrometry. The metabolites characterized were 5-(3,4-dihydroxy-1,5-cyclohexadien-1-yl)-5-ethylbarbituric acid, 5-(1-hydroxyethyl)-5-phenylbarbituric acid, 5-(3,4-dihydroxyphenyl)-5-ethylbarbituric acid as well as the previously reported 5-(4-hydroxyphenyl)-5-ethylbarbituric acid; unchanged phenobarbital was also identified. 9 references. (Author abstract)

14 MECHANISM OF ACTION: BEHAVIORAL

107117 Goodwin, F.K.; Ebert, Michael H.; Bunney, W.E., Jr. Section on Psychiatry, Laboratory of Clinical Science, NIMH, Bethesda, Md. 20014 Mental effects of reserpine in man: a review. (Unpublished paper). Rockville, Md.NIMH, 1972, 37 p.

There is considerable support for the hypothesis of reserpine as a precipitant of depressive reactions, though it is difficult to assess the specific contribution of the drug per se to the occurrence of such reactions. This finding, based on a survey of numerous studies which related reserpine to mental depression, contradicts the previous hypothesis of reserpine as the producer of depressive reactions. On the basis of an examination of the relationship between onset of depressive reactions and dose and duration of therapy with reserpine, it is concluded that development of depressive reactions in the patient may most reliably be associated with the variable of past history of affective illness. While employment of reserpine has diminished considerably since the 1950s, the drug continues to be a useful tool in neuropsychopharmacology. In view of this reevaluation, the biogenic amine hypothesis should be reconsidered. 102 references.

108445 Dundee, J.W.; Pandit, S.K. Department of Anesthetics, The Queen's University of Belfast, Northern Ireland Anterograde amnesic effects of pethidine, hyoscine, and diazepam in adults. *British Journal of Pharmacology (London).* 44(1):140-144, 1972.

The ability of premedicant drugs to suppress memory for events immediately before and for a few hours after surgery was studied. Results indicate that: 1) the intravenous administration of 5 and 10mg of diazepam caused anterograde amnesia in 50 and 90% of adults, the peak effect occurring in 2-3 min and action persisting for 20-30 minutes; 2) hyoscine (0.4and 0.6mg) caused amnesia in 35 and 50% of patients with peak effect not occurring until 50-80 min after injection and action persisting for at least 120 minutes; 3) with neither drug was there any relationship between the incidence of amnesia and the degree of drowsiness; 4) amnesia was not observed after saline or after 50mg pethidine; and 5) on questioning 6 h after a short operation, many patients had no memory of an object which they clearly recognized and described 1 h after surgery. 12 references. (Author abstract)

108642 Kraemer, Helena C.; Korner, Anneliese F.; Thoman, Evelyn B. Dept.of Psychiatry, Stanford Univ., School of Medicine, Stanford, Calif. 94305 Methodological considerations in evaluating the influence of drugs used during labor and delivery on the behavior of the newborn. ***Developmental Psychology.*** **6(1):128-134, 1972.**

Analysis of the results derived from studies concerned with the relationship between drugs administered during labor and delivery and neonatal behavior must be done so as to differentiate the effect of drugs from that of factors such as the length of labor and parity. Results of a survey of obstetrical drug management undertaken to investigate the interrelationship of drug practices and such factors suggest an appropriate method of statistical analysis which was then applied to the results of the 2 studies of newborns. Length of labor, parity, and drugs are all shown to affect behavior, with length of labor exerting the strongest influence of the particular types of behavior studied. 10 references. (Author abstract)

109669 Peters, Henry A.; Daly, Richard F.; Sato, Susumu. University of Wisconsin Medical Center, Madison, Wisconsin Reserpine for tardive dyskinesia. ***New England Journal of Medicine.*** **286(2):106, 1972.**

In view of the debate on the use of amantadine for tardive dyskinesia, the use of a high dosage of reserpine is reported which brought about almost complete control of symptoms previously resistant to therapy: in and out movements of the tongue, tremors of the jaw and dyskinesias of the pelvis. Five patients tolerated the medication without much difficulty, and the dosage of reserpine was reduced gradually after control of the dyskinesia without recurrence. The use of rauwolfia is recommended in gradually increasing dosage followed by a gradual reduction to maintenance levels. 5 references.

111296 Itil, T.M.; Stock, M.J.; Duffy, A.D.; Esquenazi, A.; Saleuty, B.; Han, T.H. Missouri Institute of Psychiatry, University of Missouri School of Medicine, 5400 Arsenal Street, St.Louis, Missouri 63139 Therapeutic trials and EEG investigations with SCH-12,679 in behaviorally disturbed adolescents. ***Current Therapeutic Research.*** **14(3):136-150, 1972.**

A centrally effective compound with a new chemical structure (d-7,8-Dimethoxy-3-methylphenyl-2,3,4,5,-tetrahydro-1H-3-benzazepine acid maleate) and an unusual electroencephalographical profile, was found to have an effect on the aggressive and violent behavior of mentally retarded adolescent females. The patients also experienced improvement in overall clinical symptomatology with an increase of learning abilities and socialization. No serious laboratory or clinical side-effects were observed in the therapeutic dosages. 13 references. (Author abstract modified)

112017 No author. author address not given The doping of athletes. ***Medical Journal of Australia (Sydney).*** **1(2):39-40, 1972.**

The taking of drugs to stimulate athletic performance in humans is discussed. A report of the Medical Commission of the British Commonwealth Games Federation on the steps taken to prevent and detect drug taking at the Ninth British Commonwealth Games in Edinburgh in 1970 is presented. Two groups of drugs are considered: substances acting on the nervous system (particularly the sympathetic amines) and anabolic steroids. Measures taken to check drug abuse were: 1) a signed declaration by each competitor that he did not indulge in drug use, 2) issuing to each competitor a statement of substances considered as dope, and 3) random testing of the urine of the competitors. 1 reference.

112081 Meares, Russell; Mills, J.E.; Oliver, L.E. University of Melbourne, Department of Psychiatry, Austin Hospital, Heidelberg, Victoria 3084 A clinical comparison of two non-barbiturate

***hypnotics, Mogadon and Mandrax. Medical Journal of Australia (Sydney).* 1(6):266-267, 1972.**

A double-blind triple cross-over investigation of the hypnotic effects of Mogadon (nitrazepam) and Mandrax (methaqualone and diphenhydramine) showed that both were superior to placebo, but there was little difference between them. This finding is discussed in the light of what is known of their relative safety. Mogadon may be safer than Mandrax and should be preferred, since no clear difference in their hypnotic effect has been demonstrated. 22 references. (Author abstract modified)

112267 O'Neal, Edgar; Kaufman, Laura. Dept.of Psychology, Tulane Univ., New Orleans, La. 70118 The influence of attack, arousal, and information about one's arousal upon interpersonal aggression. *Psychonomic Science.* 26(4):211-214, 1972.

Three determinants of the magnitude of interpersonal aggression were investigated: attack, drug induced arousal, and information regarding arousal. Under the guise of a stress and problem solving experiment, 72 male college students participated in a 2 by 2 by 2 factorial of Arousal (Dexedrine)/No Arousal (placebo) by Information (stimulant or vitamin) by Attack/No Attack. After having their solution to a problem evaluated either favorably or unfavorably via a digital counter by a confederate, Ss used electric shocks to evaluate a solution supposedly produced by the confederate. Attack and arousal each reliably increased the amount of shock delivered. Ss told that they had received a stimulant rated themselves significantly higher in tremor and palpitation but not in anger and, unexpectedly, were slightly higher in aggression than the other Ss. 16 references. (Author abstract)

112899 Hollis, John H.; St.Omer, Vincent V. University of Kansas, Parsons Research Center, Parsons State Hospital, Parsons, Kansas 67357 Direct measurement of psychopharmacologic response: effects of chlorpromazine on motor behavior of retarded children. *American Journal of Mental Deficiency.* 76(4):397-407, 1972.

The effects of graded doses of Chlorpromazine (CPZ) on motor behavior of retarded children was studied. Using direct, continuous, and automatic measurements, the effects of CPZ on 3 types of motor movements (hand, leg, and stereotyped rocking) and several types of control (free-operant, discriminated operant, fixed-ratio, variable-interval, and patellar-reflex) were studied. The results supported the hypotheses that: (a) CPZ decreases the rate of motor responding; (b) graded doses of CPZ have a graded effect on response rate; and (c) CPZ response data curves obtained from children are similar to those obtained with animals. 28 references. (Journal abstract)

112981 Domino, Edward F.; Albers, James W.; Potvin, Alfred R.; Repa, Brain S.; Tourtellotte, Wallace W. Michigan Neuropsychopharmacology Research Program, Dept.of Pharmacology, Univ.of Michigan, Ann Arbor, Mich. Effects of d-amphetamine on quantative measures of motor performance. *Clinical Pharmacology and Therapeutics.* 13(2):251-257, 1972.

The effects of 10mg.of d-amphetamine and a placebo of similar appearance were determined by means of a battery of quantitative objective measures of motor performance in normal volunteers. The medication was administered in a random, double-blind, crossover design on 2 occasions 1 week apart. No significant differences between the effects of the medications on resting and sustention tremor or precision hole steadiness were found. However, several compensatory tracking tasks which required sustained concentration and motor coordination were significantly improved with d-amphetamine. 12 references. (Author abstract)

112982 Kay, David C.; Jasinski, Donald R.; Eisenstein, Richard B.; Kelly, Orville A. NIMH, Addiction Research Center, Lexington, Ky. Quantified human sleep after pentobarbital. *Clinical Pharmacology and Therapeutics.* 13(2):221-231, 1972.

Intramuscular doses of pentobarbital (75, 150, 300mg.per 70 Kg.)and placebo were given to 8 male postaddict subjects at weekly intervals. After 4 adaptation nights, a crossover design with randomized block analysis of variance was used to demonstrate significant drug effect. Pentobarbital decreased rapid eye movement sleep (REMS) by decreasing the number and duration of REMS episodes and by delaying the onset of the first REMS episode, without measurably changing the period of the REMS cycle. Pentobarbital also decreased the prevalence of eye movements and of disruptions during REMS. Pentobarbital increased spindle (Stage 2) sleep and spindle burst incidence during Stage 2 sleep but had

minimal effect on delta (Stages 3 and 4) sleep. Pentobarbital decreased muscle tension and body movements but had little effect on EEG measures of waking state. The combined reduction of REMS and increase of spindle sleep might be used as a standard effect with which to determine equivalent doses of barbiturates and similar hypnotics. 75 references. (Author abstract)

112983 Freund, Jack; Krupp, George; Goodenough, Donald; Preston, Lester W. Dept.of Medicine, Medical College of Virginia, Richmond, Va. The doctor-patient relationship and drug effect. *Clinical Pharmacology and Therapeutics.* 13(2):172-180, 1972.

The effects of an anorexigenic agent (Dextroamphetamine) and a placebo on weight loss in 64 obese female patients were evaluated over a period of 4 weeks. Half of the patients were field dependent and half were field independent. This psychological categorization of the patients refers to individual differences in analytic functioning in perception that can be objectively evaluated and appears to parallel personality trait differences that have been noted between placebo reactors and nonreactors. An investigational drug or known drug treatment condition was created. Data from the study showed that: (1) Patients on dextroamphetamine lost more weight than patients on placebo. (2) Patients who were treated under known drug conditions lost more weight during the first week but not during the full 4 weeks. (3) Field dependent patients under known drug conditions did not lose any more weight than field independent patients under the same conditions. (4) There was considerable variation in the weight loss achieved by the patients of the same physician. 27 references. (Author abstract)

113146 Keister, Michael E.; McLaughlin, Robert J. Saint Louis University, Saint Louis, Missouri Vigilance performance related to extraversion - introversion and caffeine. *Journal of Experimental Research in Personality.* 6(1):5-11, 1972.

Sixty subjects who scored on the extremes of the introversion - extraversion dimension of the Eysenck Personality Inventory were tested on a vigilance task under either a drug (caffeine), placebo, or no drug condition. It was predicted and found that extraverts in the no drug condition showed a significant decrement in performance between the first and last third of the task. The introverts as predicted showed no decrement. As hypothesized, the drug produced differential effects on the two personality groups relative to their performance without the drug; the extraverts and introverts who were given caffeine showed no increment or decrement between the first and last third of the task. 22 references. (Author abstract)

113372 Benkert, O.; Crombach, G.; Kockott, G. Max-Planck-Institut fur Psychiatrie, Neurochemische Abteilung und Poliklinik, Munich, Germany Effect of L-Dopa on sexually impotent patients. *Psychopharmacologia (Berlin).* 23(1):91-95, 1972.

In a pilot study 10 sexually impotent patients, in whom psychic causes could be excluded to a large extent, were selected to take L-DOPA for about 12 weeks. Two had to be excluded because of side-effects. The most obvious effect was the increase in frequency of spontaneous erection during the night. A slight to moderate increase in degree of penile erection was also observed for 6 of 8 patients, but the erection ability was insufficient to consummate sexual intercourse. An increase in libido was observed in 2 patients only. Psychic changes were not found; only 1 patient showed high irritability. Five patients noticed that they could carry out their daily work more efficiently. 11 references. (Author abstract)

113799 Kales, A.; Caldwell, A.; Goring, P.; Healey, S. Milton S.Hershey Medical Center, UCLA sleep Research and Treatment Facility, Los Angeles, California Psychological evaluation and treatment studies of insomniac subjects. *Psychophysiology.* 9(1):91, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that questionnaires and psychological tests (primarily MMPI) completed by 128 insomniac subjects are being analyzed. Preliminary findings include the following: (1) the proportion of pathological or disturbed profiles in this group was at least as high or higher than the disturbed profiles seen in general psychiatric patient populations; and (2) the most consistent psychopathology present on an overall basis was a significantly high degree of depression. To a less extent, other frequent disturbances included elevated levels of hysteria, anxiety and psychopathic deviation. General and specific recommendations for treating insomnia have been described previously. It has been emphasized that

insomniac patients strongly resist seeing any of their difficulty in psychological terms and instead focus on the physical aspects. However, it was found that the majority of these patients can be treated, especially if the psychotherapist has an active and direct approach. Pharmacological treatment is often combined with psychotherapy. It has been found that flurazepam (15mg) is quite effective for both inducing and maintaining sleep; 30mg can be used in severe and protracted cases. (Journal abstract modified)

113882 Kales, A.; Dement, W.G.; Tan, T.L.; Zarcone, V.; Hoddes, E.; Carskadon, M.; Kales, J.D. Milton S.Hershey Medical Center, UCLA Sleep Research and Treatment Facility, Los Angeles, California Effects of Sinequan on sleep of insomniac subjects. *Psychophysiology.* 9(1):93, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that in 3 separate sleep laboratory studies using insomniac subjects, the effects of Sinequan on sleep were compared to placebo administration. In the first study, after placebo adaptation and placebo - baseline, 4 subjects were administered Sinequan 25mg at h.s.for a 1 week period. In the other 2 studies the protocol consisted of 4 placebo nights for adaptation and baseline purposes, 2 weeks of continuous drug administration (Sinequan 50mg each night), and 4 placebo withdrawal nights. The results for the 3 studies were quite consistent and indicate that the drug is quite effective in enhancing sleep maintenance with a slight diminution of this effect toward the end of the drug period. Further studies are necessary to determine whether the drug is effective in terms of inducing sleep and whether tolerance develops. All 3 studies showed a REM decrease with drug administration and a REM rebound following withdrawal. (Journal abstract modified)

113884 Globus, G.; Phoebus, E.; Boyd, R.; Drury, R.; Leventhal, T. University of California, Irvine, California The effect of a tranquilizer on the temporal organization of sleep. *Psychophysiology.* 9(1):94, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep the effect of a new benzodiazepine, Lorazepam, on the period and amplitude of the NREM-REM cycle, as determined by a binary autocorrelation, was investigated. Nine normal subjects were studied under baseline, drug (generally 2mg) and recovery conditions. A 1 factor analysis of variance with repeated measures was performed and orthogonal contrasts taken. The analysis of variance and contrast did not approach significance for period. However, the quadratic contrast was highly significant for amplitude and accounted for most of the variance. The lack of effect of the drug on period of the sleep cycle is consistent with other data that period is quite stable under a variety of conditions. Although variability of the rhythm as measured by amplitude is clearly affected, the behavioral significance of this disruption in temporal organization cannot be determined. Further, it seems not unlikely that a clinical population with preexisting sleep irregularity might become more regular on drug. (Journal abstract modified)

113885 Globus, G.; Phoebus, E.; Fishbein, W.; Boyd, R.; Drury, R.; Leventhal, T. University of California, Irvine, California The effect of a new tranquilizer on sleep measures and phasic integrated potentials. *Psychophysiology.* 9(1):94, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep the effect of the benzodiazepine, Lorazepam, generally at a 2mg dose, was studied over an 8 night baseline, drug and recovery design. Major findings were that the drug significantly reduced percent REM sleep but that this was not associated with rebound increases in percent REM sleep either on the last third of drug nights or on recovery nights. Effect on phasic integrated potentials followed closely changes in REM sleep. Wake time after sleep onset was significantly reduced on drug. The most noteworthy finding was that stage 3 and stage 4 sleep are not suppressed by the drug. Whether or not a reduction in REM sleep (or stage 4) which is not followed by a rebound increase has any physiologic significance is unclear. Although it is a simple matter to test the effect of drugs on sleep in the laboratory, the clinical importance of findings for the benzodiazepine group remains obscure. (Journal abstract modified)

113886 Hartmann, Ernest; Cravens, James; Stanford, Gail; Zwilling, George; Bernstein, Jacob. Boston State Hospital, Boston, Mass. Long term effect of drugs on sleep: reserpine, amitriptyline, chlorpromazine, chloral hydrate, chlordiazepoxide, placebo. *Psychophysiology.* 9(1):94, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep the preliminary results are presented of a long-term human drug study in which each subject has 6 nights of adaptation and baseline, and then takes part in 6 separate experimental periods, each period lasting 2 months. An experimental period consists of 28 days of drug administration, during which time the subject takes drug or placebo every evening, followed by 30 days without drug. The subject sleeps in the laboratory the first 5 nights on drug, then once per week while on the drug, the first 6 nights after discontinuation, then once per week for the remainder of the 2 month period. Thus, there are 17 nights of uninterrupted laboratory sleep study during a single experimental period. Reserpine (0.50mg/day) produced some increase in D-time, little effect on other variables. Amitriptyline (50mg/day) slightly increased sleep during administration. D-time was low during administration with an increase for 1 to 2 nights after discontinuation. Slow-wave sleep (SWS) usually increased. Chlorpromazine (50mg/day) produced little clear effect on sleep variables. Chloral hydrate (500mg/day) slightly increased sleep time and decreased sleep latency. Chlordiazepoxide increased total sleep and SWS early during administration. Placebo in several cases produced D-time and SWS clearly higher than on baseline (nights 4, 5, and 6), suggesting a long lasting adaptation effect. (Journal abstract modified)

113890 Vaughan, Tom; Wyatt, Richard J.; Green, Richard. National Institute of Mental Health, Rockville, Md. Changes in REM sleep of chronically anxious depressed patients given alphamethylparatyrosine (AMPT). *Psychophysiology.* 9(1):96, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep 5 chronically anxious, depressed patients (40 to 59 years old), who failed to respond to previous therapy, were given a therapeutic trial of 3g/24 hours of alphamethylparatyrosine (AMPT), a selective inhibitor of norepinephrine and dopamine synthesis. The 3 week AMPT period was preceded and followed by a week placebo period. Data during the last 5 nights of the initial placebo (P) and the first 5 nights of AMPT were collected. A trend toward increased REM sleep with AMPT was found and is in agreement with previous study of the effects of AMPT on human sleep. An interesting finding in the patients on AMPT was the failure of the EMG to diminish during REM sleep. (Journal abstract modified)

113891 Vogel, Gerald W.; Hickman, Judy; Thurmond, Arthur; Barrowclough, Barbara; Giesler, Douglas. Georgia Mental Health Institute, Georgia The effect of Dalmane (flurazepam) on the sleep cycle of good and poor sleepers. *Psychophysiology.* 9(1):96, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep the effects of Dalmane on the sleep cycle of 5 good and 5 poor sleepers (insomniacs) as defined by Monroe was investigated. The schedule involved 4 predrug nights with placebo administration, 7 drug nights, and 3 postdrug nights with placebo administration. The good sleepers were given 30mg and the poor sleepers were given 15mg of Dalmane. Drugs were administered by mouth at bedtime. It was found that Dalmane increased total sleep time in poor sleepers but not in good sleepers; reduced slow - wave sleep in good sleepers but not in poor sleepers; and did not affect REM percent during or after administration. Dalmane decreased the sleep latency of poor sleepers. For clinical purposes it should be useful to know that in a clinical dose Dalmane increased total sleep time in poor sleepers but did not prolong the sleep of good sleepers. (Journal abstract modified)

113897 Minard, James; Turek, Ibrahim; McWilliams, Jun-Ko. Maryland Psychiatric Research Center Possible 'REM-rebound' in a neonate whose mother had phenothiazine medication during pregnancy. *Psychophysiology.* 9(1):97-98, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep possible REM rebound in a neonate whose mother had phenothiazine medication during pregnancy was studied. As described in previous reports, it has been characteristic to find day to day reduction in newborns' sleeping REM (abrupt, coordinated shifts in eye position, recorded by EOG from sleeping neonates still enough so REM was not simply elicited reflexively to hand movement). Casual inspection is sufficient to show the striking departure from the general rule provided by the infant by a mother on phenothiazine medication during pregnancy. During the first interfeeding period of the night, there were 136 REMs on day 1 and 545 on day 3.

The second interfeeding period showed a similar increase from day 1 (260) to day 3 (702). REM/min sleep showed a similar change (1.64 to 5.34, first period and 1.34 to 3.60, second period). Such a REM increase is unique in the data. Psychiatrically effective dosage of phenothiazine is hypothesized to have results in the familiar REM rebound after birth. This interpretation would be consistent with previous studies using observed eye movement. Further research with neonate populations is needed. (Journal abstract modified)

114574 Pack, Allen T.; Schmidt, Helmut S. College of Medicine, Ohio State University, Columbus, OH Methysergide and sleep in human subjects. *Psychophysiology.* 9(1):88, 1972.

In a paper presented to the 11th Annual Meeting of the Association for the Psychophysiological Study of Sleep it is reported that in 2 double-blind groups, 6 subjects took 4mg of methysergide for 6 days and placebo for 9 days and 4 subjects took 6mg of methysergide for 4 days and placebo for 6 days. Sleep recordings were o btained and scored for NREM sleep stages 1, 2, 3 and 4 and REM sleep. For the 4mg group and 1 6mg subject there was a significant decrease in stage 4 during methysergide. All subjects showed an increase in REM sleep latency and a decrease in total REM sleep. By chance 3 of the 6mg subjects had minimal stage 4. This finding led to scrutiny of all results and revealed a persistent shift of NREM sleep to lighter stages as deeper stages were suppressed, i.e.,as 4 decreases, 3 increases and as 3 and 4 decrease, 2 and 1 increase. Therefore, a competitive inhibitor of serotonin delays and decreases REM sleep. Stages 1 , 2, 3 and 4 construct a sleep continuum moderated serotonin: with increasing available serotonin, sleep is spent in deeper stages; with decreasing serotonin, sleep is spent in lighter stages. (Journal abstract modified)

114907 Pivik, R.T.; Zarcone, V.; Dement, W.C.; Hollister, L.E. Dept.of Psychiatry, Harvard Medical School, Boston, MA Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clinical Pharmacology and Therapeutics.* 13(3):426-435, 1972.

A series of experiments was conducted to determine the effects of orally administered 1-trans-delta-9-tetrahydrocannabinol (THC) on both undisturbed and experimentally altered (by rapid eye movement (REM) deprivation) sleep patterns of young adult male volunteers. In the deprivation experiments, the effects of a semisynthetic delta-6a-10-THC homologue, synhexl, were also studied. In the normative studies, 4 subjects received THC in doses ranging from 61 to 258 micrograms per kilogram shortly before sleep onset, while in the deprivation experiments two subjects received either THC or synhexl the morning after the second of two consecutive nights of REM deprivation. In both normative and deprivation experiments, all night sleep recordings were taken during baseline, drug, and postdrug conditions. The results of both types of experiments were consistent in demonstrating increments in Stage 4 sleep and decrements in REM sleep. In the normative experiments, reduction in Stage 1 and time awake after sleep onset were observed at the highest dose level. Interpretation of these results and their relation to the effects of other psychoactive compounds upon sleep patterns are discussed. 34 references. (Author abstract modified)

114908 Gottschalk, Louis A.; Elliott, Henry W.; Bates, Daniel E.; Cable, Claire G. Dept.of Psychiatry and Human Behavior, College of Medicine, Univ.of California at Irvine, Irvine, CA Content analysis of speech samples to determine effect of lorazepam on anxiety. *Clinical Pharmacology and Therapeutics.* 13(3):323-328, 1972.

A study is described illustrating the use, in neuropsychopharmacologic studies, of an objective measure of psychological states, such as anxiety, through the content analysis of 5 minute samples of speech. The psychoactive drug tested was a new benzodiazepine, lorazepam. It was found to exert significant antianxiety effects as measured by the content analysis method when administered parenterally at a dosage of 5.0mg.compared to anxiety changes occurring after no drug or 3.0mg of lorazepam. Interesting physiological changes in relation to drug dose and anxiety inhibition were followed and are also reported. 8 references. (Author abstract modified)

115523 Klapper, J.A.; McColloch, M.A. Department of Neurology, University of Colorado Medical Center, 4200 East 9th Avenue, Denver, CO 80220 Personality and reactivity to stimulants and depressants. *Journal of Nervous and Mental Disease.* 154(6):439-444, 1972.

Thirty one nonpatient male volunteers with four distinct Minnesota Multiphasic Personality Inventory patterns (neurotic triad pattern, psychotic tetrad pattern, elevated mania (MA) and psychopathic deviant (Pd) scales, and normal patterns) were selected in order to investigate the differential effect of stimulants and depressants on different personality types. Two stimulants, caffeine sodium benzoate and methylphenidate hydrochloride, and two depressants, secobarbital sodium and amobarbital sodium, were given to various combinations of the four types of subjects. The subject's scores on two cognitive and one motor test following drugs administration were compared. The group with the psychotic tetrad pattern was found to be relatively unresponsive to stimulants and sensitive to depressants. Those subjects with the elevated Ma and Pd pattern were generally very responsive to stimulants and more sensitive to depressants than the normal group and the group with the neurotic triad pattern. The group with the neurotic triad pattern was relatively responsive to stimulants, but less sensitive to depressants than subjects with the psychotic tetrad or the elevated Ma and Pd pattern. Results are discussed in terms of Eysenck's theory of drug response based on an extroversion -introversion dimension. The group of subjects with the elevated Ma and Pd profile had personality scores suggestive of extroversion. 11 references. (Author abstract modified)

115586 Buckley, Robert E. 2014 Park Street, Livermore, CA 94550 A neurophysiologic proposal for the amphetamine response in hyperkinetic children. ***Psychosomatics.*** **13(2):93-99, 1972.**

A neurophysiological proposal for the amphetamine response in hyperkinetic children is made, based on clinical observations and laboratory research. It appears that these children probably have a deficiency of the neurophysiologic mechanisms which control and inhibit temporal lobe activity. Their hyperactivity is similar in some ways to the behavior of patients with psychomotor temporal lobe seizures. When the ventromedial nucleus of the hypothalamus is inhibited the lateral and the medial posterior area will be released for increased activity. Amphetamine drugs activate the ventromedial nucleus when it is inhibited by barbiturate anesthesia. It is proposed that amphetamine also activates the ventromedial nucleus when it is inhibited by a disturbance of temporal lobe function. This proposal allows differentiation between the minimal brain damaged child whose impulsive behavior is paradoxically improved by amphethamine, and the organically normal behavior disorder group who may have increased disorder when given amphetamine. Amphetamine helps increase the activity of an organically inhibited ventromedial nucleus. It will simultaneously activate the reticular system. The beneficial effect of amphetamine appears to be limited to the increased ability to concentrate and to respond to discipline. The minimal brain disorder which caused the hyperactivity may continue to cause difficulties as the child matures. 36 references. (Author abstract modified)

115827 Yamamoto, Joe; Kline, Frank M.; Burgoyne, Rodney W. University of Southern California School of Medicine, Los Angeles, CA 90033 Double-blind drug study in depressed outpatients. ***Rocky Mountain Medical Journal.*** **69(4):71-74, 1972.**

A double-blind controlled comparison of the treatment of 48 depressed psychiatric outpatients with amitriptyline and diazepam is reported. The results show some degree of effectiveness (41% with amitriptyline; 40% with diazepam) with both drugs. 10 references.

115973 no author. no address Taming a tic with a tranquilizer. ***Medical World News.*** **13(8):29, 1972.**

Treatment of Gilles de la Tourette's disease, an unusual form of generalized tic, with haloperidol, a tranquilizer is described. Dosages ranging up to 180mg daily are titrated against decrease of symptoms and side effects. Despite the large doses that may be needed initially, a remission can be maintained on doses as low as 3mg/day. It is suggested that haloperidol decreases the uptake of dopamine in the neuron.

115996 no author. no address Marijuana clouded their recent memory. ***Medical World News.*** **13(17):18, 1972.**

Marihuana impairment of recent memory is documented. In tests one half hour after the start of smoking, marihuana smokers suffered a significant disruption of ability to remember in detail a story read to them or to remember the facts in chronological order. This reflects the characteristic time sense disorder produced by marihuana.

116038 Griffiths, William J.; Lester, Boyd K.; Coulter, Joe D.; Williams, Harold L. Dept.of Psychiatry, University of Oklahoma Medical Center, 800 Northeast 13th Street, Oklahoma City, OK 73104 Tryptophan and sleep in young adults. ***Psychophysiology.*** **9(3):345-356, 1972.**

The effects of moderate (7.5g) and larger (12g) doses of L-tryptophan on the EEG sleep patterns of 21 normal young males were investigated. Moderate doses produced sedative effects (reports of extreme drowsiness and reduced time awake) accompanied by increased slow-wave sleep. The only effects on REM parameters were a trend (in some Ss) to early onset of stage REM, a small decrease in the period of the REM cycle, and decreased density of rapid eye movements. With the high dose, Ss again reported extreme drowsiness, and time to sleep onset was decreased. However, changes in slow wave sleep and waking time appeared only as nonsignificant trends. In the high dose group, percent of REM sleep was markedly increased, due to early onset of stage REM and to increased duration of REM episodes during the second half of the night. EEG sleep patterns on recovery nights following large doses of tryptophan were not systematically different from baseline nights. These results indicate that the changes in sleep patterns produced by L-tryptophan, presumably acting through 5-hydroxyindole pathways, are dependent on dose. The findings are consistent with the idea that serotonin, or one of its metabolites, is involved in the mechanisms controlling both SW and REM sleep. 33 references. (Author abstract modified)

116855 Jaffe, J.; Dahlberg, C.C.; Luria, J.; Breskin, S.; Chorosh, J.; Lorick, E. William Alanson White Institute, New York, NY Speech rhythms in patient monologues: the influence of LSD-25 and dextroamphetamine. ***Biological Psychiatry.*** **4(3):243-246, 1972.**

The influence of d-lysergic acid diethylamide (LSD-25) and dextroamphetamine (DA) on speech rhythms in patient monologues was investigated. Seven patients received LSD, DA and a placebo (P) over an average period of about one and one half years. A patient by drug analysis of variance was performed on mean pause time (MPT) and mean vocalization time (MVT) of verbal behavior. Monologues were recorded: 1) just prior to drug ingestion; and 2) just prior to the test session (2.5hours later). Speakers differed significantly on both measures in the first monologues, prior to the drug effect. MPT was the more discriminating interindividual measure. MPT did not change in the first monologue but was significantly different in the second monologue for all three drug comparisons. An increase of MPT without significant change in MVT indicated slowing of speech. Speech was slowed with LSD and increased with DA. 8 references.

116937 Wender, Paul H. Laboratory of Psychology, National Institute of Mental Health, Building 10, Room 2N222, Bethesda, MD 20014 The control of children's behavior with medication. Bethesda, Md.NIMH, 1972, 16 p.

The control of minimal brain dysfunction (MBD) in children with medication is discussed. The factual issues involved are considered: the types of psychological functioning that are altered by drugs in children, and the types of alteration which are produced by drugs. Philosophical questions related to the field are sketched briefly, with emphasis on the problems in the treatment of MBD and the problems associated with the problems. Although treatment with medication clearly modifies the signs and symptoms of the disorder on a short term basis, it is concluded that whether chronic treatment modifies or prevents the development of later problems, whether it has any permanent effects on the life history of the individual, remains to be determined.

117135 Hurst, Paul M.; Bagley, Sallyann K.; Ross, Sherman. Institute for Research, 257 S.Pugh St., State College, PA 16801 Effects of alcohol and methylphenidate on complex judgments. ***Psychological Reports.*** **31(1):59-67, 1972.**

In a study of the interaction of cognitive effects with mood related influences, methylphenidate hydrochloride, (12mg/70kg and 20mg/70kg), ethyl alcohol (60g/70kg), and a placebo (lactose) were given to 50 college student volunteers. Each S received each treatment once during four separate sessions, and treatment order was counterbalanced. Ss were experienced bridge players, who were given sets of bidding problems, which varied in storage load, ambiguity level, and answer format (open ended vs multiple choice). Performances were scored according to 1) frequency of active bids vs passes, and 2) a figure of merit assigned to each possible response, as developed from expert consensus. Ss wrote impromptu editorials on assigned topics from which word count measures of verbal production were

derived, and also made periodic self-ratings on mood adjective check lists. No significant drug effects were found on bidding accuracy, although methylphenidate increased the frequency of nonpasses. Alcohol produced significant efforts on eight mood clusters while methylphenidate produced little or no measurable effect. Verbal production, however, was reliably increased by methylphenidate but not significantly affected by alcohol. 8 references. (Author abstract modified)

117607 Campbell, H.; Cline, W.; Evans, M.; Lloyd, J.; Peck, A.W. Univ.of Wales, Dept.of Medical Statistics, Cardiff, Wales Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. *British Journal of Pharmacology (London).* 44(2):369P-370P, 1972.

A comparison of the effects of dexamphetamine and 1-benzylpiperazine was made with Ss formerly addicted to amphetamine and similar drugs. Eighteen volunteers completed a questionnaire designed to ascertain whether they felt drug effects. The scores to questions indicating an amphetamine like effect and a liking for this effect were highest after 1-benzylpiperazine, lower after dexamphetamine and lowest after the placebo. Objective assessment of behavior using the psychiatric rating scale revealed a difference between both drugs and placebo on the excitation scale, but no difference between the two drugs. The simple questionnaire gave a similar result. The rise in pulse rate and blood pressure was greater after both drugs than for placebo. 3 references.

117936 Haddock, Samuel T. no address Usefulness of methylphenidate. *New England Journal of Medicine.* 286(7):375, 1972.

In a letter to the editor the use of methylphenidate in minimal have behavior disorders characterized by hyperactivity, reading disability, and learning defects. Nortriptyline hydrochloride is prescribed for night use and seeks to increase the patients' self-confidence. The hyperkinetic child who is denied stimulant drug therapy through fear of addiction may be more predisposed to drug abuse as an adolescent than his stimulant treated counterpart. 4 references.

118480 Wyatt, Richard J. NIMH, St.Elizabeths Hospital, Washington, DC 20032 Sleep, serotonin, and schizophrenia. (Unpublished paper). Washington, DC, NIMH, 1972, 1 p.

The relationship between serotonin, sleep and schizophrenia is examined. Parachlorophenylalanine (PCPA), a drug which inhibits tryptophan hydroxylase and consequently lowers brain serotonin, produces changes in REM similar to those seen in schizophrenia. Chloropromazine and the precursor to serotonin, 5-hydroxytryptophan (5-HTP) reverse these effects. Preliminary results of a clinical trial of 5-HTP in chronic schizophrenic patients is discussed. (Author abstract modified)

118553 Reiss, David Section on Experimental Group and Family Studies, Adult Psychiatry Branch, Bethesda, MD The resilience of family process: effect of secobarbital II. Social mechanism of drug action. (Unpublished paper). Bethesda, MD, NIMH, 1972, 23 p.

Five alternate explanations for the impact of secobarbital on family problem solving are delineated. Secondary data analysis was performed in order to determine whether the speech changes, produced by the drug, represented compensatory process in the family or were passive responses to speech changes, induced by the drug, in the offspring. Data analysis strongly suggests that the speech changes reflected an increase in communication efficiency that rapidly compensated for the subtle, socially isolating effects of the psychoactive drug. The analysis supports a view of family process as being very sensitive to small changes in its members but that these changes in family process can, themselves, be quickly returned to their usual levels by compensatory processes. 14 references. (Author abstract)

118802 Bond, Alyson J.; Lader, Malcolm H. Institute of Psychiatry, University of London, De Crespigny Park, Denmark Hill, London, S.E.5, England Residual effects of hypnotics. *Psychopharmacologia (Berlin).* 25(2):117-132, 1972.

Ten normal subjects were tested on a large battery of physiological and psychological tests 12 hours after a hypnotic dose of butobarbitone sodium (100 or 200mg) or nitrazepam (5 or 10mg) and compared with a placebo. The subjects received all 5 treatments in a balanced design. The tests used included self-ratings, the electroencephalogram, the auditory electroencephalographic evoked response, reaction time, tapping, card sorting and the digit symbol substitution test. Both drugs were effective hypnotics according to the ratings but butobarbitone had more subjective

'hangover' the following morning. The electroencephalogram showed significant changes after both drugs but the evoked response was affected most by 10mg nitrazepam. The psychological tests showed some dose-related impairment after both drugs. Bioassay statistics suggested that with respect to these residual effects the relative potency of nitrazepam to butobarbitone was 27:1. 19 references. (Author abstract)

15 TOXICOLOGY AND SIDE EFFECTS

105607 Mintz, Morton. author address not given Drug linked to 3 babies born armless. *Washington Post.* March 4, 1972, p.A1, A17.

After 3 Australian infants were born without arms, Dr.William G. McBride of Sydney reports the possibility that imipramine, administered to the pregnant mothers during the first 3 months of pregnancy may be a directly linked cause. Similar cases have been reported from Germany, Belgium and Switzerland, in which babies were born without arms or legs, apparently as a result of imipramine or thalidomide. The FDA in the United States has required the use of warning labels on imipramine since 1965, although scientifically no cause-effect relationship has been irrefutably established. The use of other tricyclic compounds has been recommended as sedatives when the need is evident during pregnancy. The list includes: Amitriptyline (Elavil), desipramine (Norpramine, Pertofrane), doxepin (Sinequan), nortriptyline (Aventyl) and protriptyline (Vivactil).

107587 Crittenden, Frank M., Jr. Portsmouth, Va. Thioridazine incontinence. *Journal of the American Medical Association.* 219(2):217, 1972.

The case of a 49 year old man is cited to confirm the association of urinary incontinence with the use of thioridazine. Substitution of diazepam resulted in stoppage of the incontinence within a few days.

107590 Serafetinides, E.A. Dept.of Psychiatry, The UCLA School of Medicine, California Assessing the sexual side effects of psychotropic drugs. *Hospital Physician.* 8(1):58-60, 1972.

Although studies under controlled conditions of the sexual side effects of psychotropic drugs have been rare, the widespread use of such drugs has given rise to numerous reports of inhibition of ejaculation, impotence and/or decreased libido in men and inability to reach orgasm, loss of clitoral, vaginal, and uterine sensations, loss of libido, galactorrhea, and amenorrhea in women. Consequently, it is important that the psychiatrist balance the patient's need for normal sexual activity against the need for symptomatic improvement. Drugs which have been reported to engender sexual side effects are listed. Guidelines for the prescription of psychotropic drugs are suggested. 28 references.r

107692 O'Connell, G.J.; Campbell, P.B.; Ananth, J.V. Dept.of Psychiatry, St.Mary's Hospital, 3830 Lacombe Ave., Montreal 249, P.Q., Canada Amitriptyline: initial intolerance and subsequent psychosis. *Canadian Medical Association Journal (Toronto).* 106(3):115, 1972.

In a letter to the editor, a case is cited in which toxic psychosis with hallucinations was associated with amitriptyline therapy. Since the patient had evidenced an initial intolerance to a small dose of amitriptyline, it is important in such cases to use caution in prescribing higher dosages. 5 references.

107772 Lapierre, Y.D. Hospital Pierre Janet, Hull, P.Q., Canada Lithium intoxication. *Canadian Medical Association Journal (London).* 106(3):112, 1972.

In a letter to the editor an explanation is suggested for the severe lithium intoxication reported in a study by Aoki and Ruedy. Recent studies have demonstrated that water and sodium depletion precipitated by dietary salt restriction plus a salt losing diuretic will contribute to rapid increases in serum lithium levels at usual doses. Recent studies in which patients relapsed into mania following cessation of lithium treatment suggest the effect of pathophysiological factors rather than psychological factors in manic-depressive psychosis. 4 references.

107773 Aoki, Fred Y.; Ruedy, John R. Division of Clinical Pharmacology, Montreal General Hospital, Montreal 109, P.Q., Canada Lithium intoxication. *Canadian Medical Association Journal (Toronto).* 106(3):112, 1972.

In a letter to the editor responding to Lapierre's suggested explanation of lithium intoxication, it is pointed out that there is no absolute relationship between serum lithium concentrations and clinical symptoms and signs of intoxication. The importance of clinical examination in diagnosing lithium intoxication is therefore stressed. 4 references.

107799 Goldfield, Michael D.; Weinstein, Morton R. American Register of Lithium Babies, Langley Porter Neuropsychiatric Institute, San Francisco, California 94122 Suggested schedule of lithium administration during pregnancy. ***Lancet (London).*** **1(7742):152, 1972.**

Comments are offered on 2 recent reports which indicate that lithium can be highly teratogenic in laboratory rodents when large quantities are given in single doses. The apparent hazard to the developing mammalian fetus from large doses of lithium is noted, and the importance of the even distribution of dosage over time if lithium has to be given during pregnancy is emphasized. Teratogenic and other potentially toxic effects are determined not only by the amount of lithium given per day, but also by the production of transient lithium concentrations on both sides of the placenta as a result of excessive individual doses. Small divided doses administered 5 or 6 times per day are suggested in pregnancy. 9 references.

108938 Davis, Larry E.; Wesley, Richard B.; Juan, David; Carpenter, Charles C.J. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 'Locked-in syndrome' from diazepam toxicity in a patient with tetanus. ***Lancet (London).*** **1(7741):101, 1972.**

Although diazepam, in high doses, can be a useful adjunct in the treatment of severe tetanus, awareness of its potential neurological side effects is necessary and tetraplegic mutism must be added to this list. In the treatment of tetanus, no standard dosage should be used and the drug dosage should be titrated every 2 to 4 hours to achieve the minimum dose necessary to control severe muscle spasms while maintaining maximum alertness. A case report of side effects from diazepam in treating tetanus is reported. (Author abstract modified)

111341 Raskin, Allen. Psychopharmacology Research Branch, NIMH, 5600 Fishers Lane, Rockville, Maryland 20852 Adverse reactions to phenelzine: results of a nine-hospital depression study. ***Journal of Clinical Pharmacology and New Drugs.*** **12(1):22-25, 1972.**

Patient reaction to phenelzine was studied in a 9 hospital depression study conducted by the National Institute of Mental Health. Results of the study show that of patients who were placed on low tyramine content diets, there were few serious phenelzine side effects, and none of the 110 phenelzine patients had to be terminated for a hypertensive crisis. 4 references. (Author abstract modified)

112548 Ramsey, T.Alan; Mendels, Joe; Stokes, James W.; Fitzgerald, Roy G. author address not given Lithium carbonate and kidney function: a failure in renal concentrating ability. ***Journal of the American Medical Association.*** **219(11):1446-1449, 1972.**

Three patients with manic-depressive illness who were successfully treated with lithium carbonate developed polyuria and polydipsia at varying periods after starting treatment. Water deprivation studies revealed a defect in renal concentrating ability which was not corrected by the administration of vasopressin injection. None of the patients had elevated urine volumes prior to lithium carbonate therapy, and there was no evidence of other conditions which might have affected renal concentrating ability. 18 references. (Author abstract)

112629 Matthew, Henry; Roscoe, Peter; Wright, Noel. Regional Poisoning Treatment Centre, The Royal Infirmary, Edinburgh Acute poisoning: a comparison of hypnotic drugs. ***Practitioner (London).*** **208(1244):254-258, 1972.**

A report of 2.5year's experience of poisoning by barbiturates, methaqualone with or without diphenhydramine, nitrazepam, glutethimide, ethchlorvynol, carbromal with pentobarbitone, and chloral derivitives is presented. Nitrazepam should be the hypnotic of choice for all patients who are at risk from overdosage. 23 references.

112661 Farquharson, S. Department of Anaesthetics, Westminster Hospital, London S.W.1 Poisoning by tricyclic drugs. ***British Medical Journal (London).*** **1(5796):378, 1972.**

A letter to the editor discusses an aspect of treatment of overdose with tricyclic antidepressants which had not been included in a previous paper. Severe cases may show a profound metabolic acidosis often with considerable hypokalemia, both of which further predispose to major cardiac dysrhythmias. Treatment, as expected, should be with alkali and intravenous potassium, often in massive quantities. It is strongly recommended that frequent electrolyte and blood gas analyses be made in all such cases, so that supportive therapy may be given where indicated. 2 references.

112693 Cairncross, K.D. Macquarie University, North Ryde, Australia The tricyclic antidepressants. *Medical Journal of Australia (Sydney).* 1(8):388, 1972.

A letter to the editor discusses cardiovascular complications associated with amitriptyline (Tryptanol) therapy. Attention is called to a report urging careful control of imipramine (Tofranil) in patients with cardiovascular disease, and the fact that the peripheral pharmacological properties of the tricyclic antidepressant drugs are virtually identical. 1 reference.

113135 Brown, K.G.E.; McMichen, H.U.S.; Briggs, D.S. Evelina Children's Hospital, Southwark Bridge Road, London S.E.1, England Tachyarrhythmia in severe imipramine overdose controlled by practolol. *Archives of Disease in Childhood (London).* 47(251):104-106, 1972.

A 2 1/2-year-old boy, comatose and having fits after an overdose of imipramine, suffered a respiratory and cardiac arrest from which he was successfully resuscitated. A severe tachyarrhythmia was well controlled by intravenous practolol, and it is suggested that practolol is the drug of choice in this situation. 15 references. (Journal abstract)b

113775 Lang, P.G.; Talman, W.T., Jr.; Hunt, W.B., Jr. Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Va. 22901 Drug overdosage due to glutethimide: a reappraisal of management. *Southern Medical Journal.* 65(4):413-416, 1972.

A case of severe glutethimide overdosage (coma for 80 hours) managed in a respiratory care unit is presented. Prompt intubation and attention to the details of respiratory care during the long coma, analyses of arterial blood gas, chest physiotherapy and the immediate availability of management by ventilator at the onset of apnea were the decisive factors in the recovery of the patient. A review of recent clinical experience with glutethimide suggests that routine hemodialysis is not indicated for the treatment of glutethimide poisoning but should be reserved for patients with compromised renal function or hypotension resistant to other forms of treatment. 12 references. (Author abstract modified)

114545 Geerlings, P.J.; Silbermann, R.M.; Schalken, H.F.A. Psychiatric Dept., Wilhelmina Gasthuis, le Helmersstraat 104, Amsterdam, The Netherlands Acute adverse reactions to drug-taking. *Acta Psychiatrica Scandinavica (Kobenhavn).* 48(1):22-29, 1972.

A study was made of 305 psychiatric patients who were seen for emergencies diagnosed as acute adverse reactions to drugs. The psychiatric states were classified according to the CHAM system, the agent used was determined, and results were analyzed. Alcohol was the major problem (37%), and most hospital admissions were associated with the use of alcohol or lysergic acid diethylamide (LSD) and similar substances. Although a certain pathological condition was noted, almost every psychiatric state may be encountered after the use of each of the psychotrophic drugs. It is concluded that a specific LSD, amphetamine, or cannabis psychosis does not exist. 8 references. (Author abstract modified)

115177 Grove, Lynn; Crammer, J.L. St.John's Hospital, Stone, Aylesbury, Bucks, England Benzhexol and side effects with long-acting fluphenazine therapy. *British Medical Journal (London).* 5795:276-279, 1972.

The incidence of side effects of benzhexol in patients under chronic treatment with fluphenazine enanthate was investigated. Sixteen patients who had for some months been on fluphenazine enanthate injections every two or three weeks, with daily oral benzhexol were divided into two groups comparable in age, diagnostic category, and drug dose. Placebo was substituted under blind controlled conditions for benzhexol in one group, and both groups were regularly assessed by Simpson rating scale for extra pyramidal signs, and by a 30 question symptom check list. Both assessments were found reliable. Four out of eight patients had severe reactions when off benzhexol, but symptoms such as tremor and daytime sleepiness were unaltered in all patients. The other four did not suffer adversely from withdrawal of benzhexol. Acute withdrawal is therefore unjustified, but occasional revision of dosage of anti-Parkinsonian drugs is advisable. There is no evidence that tolerance develops to any effect of a phenothiazine, but long continued benzhexol might induce a denervation supersensitivity. It is also possible that Parkinsonian signs are dependent on affective state. 14 references. (Author abstract)

115180 Gould, W.M. Shanta Bhawan Hospital, Katmandu, Nepal Central nervous disturbance

with pentazocine. *British Medical Journal (London).* 5795:313v314, 1972.

In a letter to the editor a case history of central nervous disturbance treated with pentazocine is reported. The patient was hallucinating, very anxious, and apprehensive. This side effect is extremely rare and pentazocine is an otherwise excellent analgesic.

115187 Ramsden, P.D.; Froggatt, D.L. Nuffield Department of Surgery, Radcliffe, Infirmary, Oxford, England Idiosyncratic responses to phenothiazines. *British Medical Journal (London).* 1(5794):246, 1972.

In a letter to the editor, the side effects of the phenothiazine group of drugs, and in particular of perphenazine, an antiemetic are discussed. Three cases are reported in which acute extrapyramidal symptoms developed after treatment for nausea by a single dose of perphenazine. In these cases the following diagnoses were considered: epilepsy, hysteria, tetany, and tetanus. Only a small dose of perphenazine had been given. Intravenous benztropine methanesulfonate gave complete relief of symptoms. The signs and symptoms of idiosyncratic responses to phenothiazine drugs often cause confusion in diagnosis, for two reasons. Firstly, they are not commonly found as an acute phenomenon. Secondly, in the acute situation the symptoms produced mimic extremely well other serious conditions. Phenothiazine derivatives are well known to cause extrapyramidal symptoms when used over a long period, but there are few reports of an acute episode. 2 references. (Author abstract modified)

115190 Allan, R.N.; White, H.C. General Hospital, Birmingham B4 6NH, England Side effects of parenteral long-acting phenothiazines. *British Medical Journal (London).* 1(5794):221, 1972.

A hypothalamic syndrome induced inadvertently by long acting phenothiazines is reported in this case study. The long acting phenothiazine fluphenazine enanthate has been valuable in reducing the incidence of relapse in schizophrenic patients. The patient also developed extrapyramidal features which are sometimes associated with long acting phenothiazine treatment. These side effects are related to age, sex, and dose but in addition there is an individual sensitivity factor. The dose given was considerably greater than that usually recommended. The diagnostic difficulties that may be encountered in patients receiving long acting phenothiazines, particularly if on admission the past medical history is not known. Because these drugs are rarely prescribed in the general hospital setting their side effects are less well known and may escape recognition. The diagnosis of long acting phenothiazine induced side effects should be considered in patients who present with stupor, disturbance of temperature regulation with no evidence of underlying infection, and extrapyramidal signs. 3 references.

115296 Patrick, M.J.; Tilstone, W.J.; Reavey, P. Division of Medical Paediatrics, Stobhill General Hospital, Glasgow, Scotland Diazepam and breast-feeding. *Lancet (London).* 1(7749):542-543, 1972.

In a letter to the editor, a case report is presented in which diazepam being taken by a mother was transferred to a child during breast feeding. The baby became lethargic and lost weight. When breast feeding was discontinued, the baby became normal. Clinical, biochemical, and electroencephalographic data are given. Oxazepam was detected in the child's urine.

115297 Boston collaborative drug surveillance program. 400 Totten Pond Road, Waltham, MA 02154 Adverse reactions to the tricyclic-antidepressant drugs. *Lancet (London).* 1(7749):529-531, 1972.

Data from a drug monitoring program were analyzed to determine the frequency of adverse reactions attributed by physicians to the tricyclic - antidepressant group of drugs. The overall adverse reaction rate was 15.4%, and major adverse reactions such as psychosis, hallucinations, disorientation, and agitation occurred in 4.6% of 260 patients. Data from 80 patients with preexisting cardiovascular disease were analyzed to investigate a postulated association between these drugs and cardiotoxic effects. There was no evidence of such an association, and the mortality rate in this group was similar to that in the control group. 6 references. (Author abstract modified)

115527 Gilbert, James J.; Benson, Frank D. Department of Neurology, Boston University College of Medicine, 720 Harrison Avenue, Suite 407, Boston, MA 02118 Transient global amnesia: report of two cases with definite etiologies. *Journal of Nervous and Mental Disease.* 154(6):461-464, 1972.

Two cases of transient global amnesia with unrelated etiologies and their relationship to the mechanism of this syndrome are discussed. One patient with a history of migraine lends support to the hypothesized vascular mechanism for transient global amnesia. A second patient suffered an episode of transient global amnesia secondary to drug (diazepam) intoxication. It is suggested that transient global amnesia does not result from a single etiology but represents the singular manifestation of diverse mechanisms. 24 references.

115532 Davidson, N. Department of Physiology, Marischal College, University of Aberdeen, Aberdeen, Scotland Alpha rhythms and hyperkinesis. ***Nature (London).*** **238(5358):43, 1972.**

A report on 'Alpha Rhythms in the Hyperkinetic Child' by Shetty is discussed. The only conclusion which can be drawn from this report is that central nervous stimulants such as amphetamines, which are well known to increase the magnitude of physiological tremor, also increase the alpha rhythm power range. This provides no direct information concerning the neurophysiological substrate of hyperkinesis although it does support Lippold's hypothesis that oscillation in striate muscle control systems is the source of alpha rhythm and that a tendency for overall change in muscle control systems will be paralleled by changes in the alpha signal. 11 references.

115654 Litvak, Ronald; Kaelbling, Rudolf. Department of Psychiatry, Ohio State University Hospitals, 473 West 10th Avenue, Columbus, OH 43210 Dermatological side effects with psychotropics. ***Diseases of the Nervous System.*** **33(5):309-311, 1972.**

The results of an anterospective survey to assess the course of skin lesions attributable to psychotropic drug (tranquilizers and antidepressants) use are presented. Not one case of icterus was found among almost 700 patients on psychotropic medication. Less than 2.2% had abnormal liver function tests. The mild and temporary nature of skin reactions is noted. Skin reactions and lesions are a relatively frequent manifestation of an untoward reaction to psychotropic drugs, appearing in about 5% of cases. It was not possible to single out any predictive factors indicative of a greater vulnerability to drug induced skin reactions in the patient, nor was it possible to determine any specific drugs or dosages more likely to produce a skin reaction. 2 references. (Author abstract modified)

115663 no author. no address LSD and gangrenous hand infection. ***Medical World News.*** **13(15):50G, 1972.**

A case report of gangrenous infection resulting from a minor scratch on the hand and the vasoconstrictive action of lysergic acid diethylamide (LSD) is given. As with other ergot alkaloids, prolonged and frequent use of LSD may produce profound peripheral ischemia, particularly if the individual has an unusual sensitivity to these compounds. If, in addition, the individual is a heavy cigarette smoker, as was this patient, then the severity of the ischemia is further increased by the peripheral vasoconstriction due to absorbed nicotine.

115830 no author. no address Psychotropic agents and the hyperkinetic. ***Medical World News.*** **13(9):60 O, 1972.**

Discussions on the use of psychotropic drugs for the hyperkinetic child by a group of pediatricians and psychiatrists at the Ninth Annual International Conference of the Association for Children with Learning Disabilities are reported. Caution in drug therapy was stressed. Side effects are the rule rather than the exception; amphetamines and phenothiazines are perpetrators of appetite disorders and methylphenidate is a causative agent in oversedation. Drug treatment alone is seldom a sufficient remedy for a child's total set of symptoms and his maladaptive behavior; careful educational, psychological, and medical care are often required as part of a therapeutic program. Clinical trials were also reported.

115907 Ebido, Bernadito; Weinreich, Avron; Lipton, Barbara. Department of Anesthesiology, The Mount Sinai School of Medicine of the City University of New York, New York, NY Anesthetic agents and neuropsychiatric complications following extracorporeal circulation. ***Bulletin of the New York Academy of Medicine.*** **48(3):545-557, 1972.**

To determine whether the choice of anesthetic agent influenced the postoperative incidence of neuropsychiatric complications after cardiopulmonary bypass, 100 consecutive patients who had undergone operation were studied. These patients received in combination with nitrous oxide either morphine sulfate, Innovar (droperidol and fenta-

nyl), or halothane as anesthetics. The incidence of neuropsychiatric complications (18%, 24%, and 23%respectively) was not significantly different among the three groups. Although there was a much higher incidence of hypotension during cardiopulmonary bypass when halothane was used, this did not result in an increased incidence of neurologic complications. Two factors appeared to influence the postoperative neuropsychiatric condition: age and the type of surgical procedure. Patients in the older groups and those who had had prosthetic valve replacements showed a greater incidence of postoperative neuropsychiatric complications. The reasons for these findings are discussed. 25 references. (Author abstract modified)

117105 Dillenkoffer, Robert L.; Gallant, Donald M.; Phillips, John H. Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, LA Electrocardiographic evaluation of mesoridazine (Serentil). ***Current Therapeutic Research.*** **14(2):71-72, 1972.**

The EKG effects of mesoridazine (Serentil) administered to nine chronic schizophrenics are reported. The global ratings of improvement at termination showed five patients as slightly improved, three as moderately improved, and the remaining patient as unchanged. All of the patients had normal EKG tracings at baseline evaluation. At a dosage of 75mg daily of mesoridazine, four of nine patients showed mild to moderate EKG abnormalities. At a maximal dosage of 300mg daily, all of the nine patients showed moderate to marked changes. Eight of these nine abnormal EKG tracings returned to normal two weeks after cessation of therapy. It is suggested that mesoridazine as well as thioridazine, when given in recommended dosages, is almost uniformly associated with abnormalities of myocardial repolarization. These changes can occur even when the dosage is well below optimum therapeutic level. Patients treated with thioridazine and mesoridazine should be followed with periodic EKG's even when the daily dosage is low. 3 references. (Author abstract modified)

117107 Crombie, D.L.; Pinsent, R.J.F.H.; Fleming, D. Royal College of General Practitioners, London, S.W.7, England Imipramine in pregnancy. ***British Medical Journal (London).*** **1(5802):745, 1972.**

In a letter to the editor the findings of the Royal College of General Practitioners' survey on imipramine use in pregnancy is reported. Among over 8,000 women whose pregnancies lasted beyond the 27th week, there were 19 prescriptions issued for imipramine during these early weeks. No abnormalities in this group were reported at birth, nor subsequently. Another 28 prescriptions for amitriptyline were issued. Twenty seven were associated with babies who appeared to be normal in all respects. One baby was described as showing at birth swelling of hands and feet of unknown etiology. The prescription for amitriptyline had been issued in the sixth week after the last menstrual period; a total of six 25mg tablets was consumed. Subsequent inquiry at the age of two years established that the child's limbs were by then normal in all respects and that no other specific malformation had been detected by the general practitioner nor the consultant pediatrician concerned.

117109 Marsden, P.; Sheldon, Joanna. Royal Sussex County Hospital, Brighton, Sussex, England Acute poisoning by propylhexedrine. ***British Medical Journal (London).*** **1(5802):730, 1972.**

A case of extreme illness resulting from ingestion of the contents of a nasal inhaler containing propylhexedrine, a sympathomimetic amine, is reported. The patient suffered a myocardial infarction and frequent ventricular extrasystoles which are similar to abnormalities reported after the administration of noreadrenalin. The illness was followed by the syndrome of shock lung. The pathogenesis of the condition has not been fully elucidated. The patient was started on prednisone after the syndrome had developed and made a dramatic recovery suggesting that this may be the treatment of choice. 4 references. (Author abstract modified)

117112 Dillon, J.B. no address Parenteral long-acting phenothiazines. ***British Medical Journal (London).*** **1(5803):807, 1972.**

In a letter to the editor, a case of a pyrexial reaction occurring with no more than an average dose of fluphenazine decanoate (a phenothiazine) is reported. The man had also received haloperidol. Pyrexia does not appear to have been recorded in the literature as a complication of haloperidol treatment.

117113 Coppel, D.L.; Dundee, J.W. The Royal Victoria Hospital, Belfast, Ireland Psychosis and ketamine. ***British Medical Journal (London).*** **1(5803):805, 1972.**

In a letter to the editor it is suggested that ketamine is best used without any depressant premedication, otherwise its distinct pharmacological properties will be reduced and recovery prolonged. The unpleasant postoperative sequelae can be effectively blocked by the use of diazepam given at the end of operative procedure. Ketamine is not the drug of choice for electroconvulsive therapy procedures. By using ketamine the doctor exposes a patient not only to the disadvantages of a long recovery period but also the possibility of unpleasant dreams and delirium, which do not exist with conventional anesthesia for electroconvulsant therapy. 3 references.

117559 no author. no address Heart disease and tricyclic antidepressants. ***World Medicine (London).*** **7(19):67, 1972.**

Three cases are discussed in which unexplained cardiac failure was associated with earlier treatment with a tricyclic antidepressant drug. Possible explanations include the high affinity of these drugs for cardiac musculature, and the action of these drugs on endogenous catecholamines. 2 references.

117572 Weinstein, Morton R.; Fischer, Ames. no address Benztropine toxicity and atropine psychosis. ***Journal of the American Medical Association.*** **220(12):1616-1617, 1972.**

Antiparkinsonian drugs combined with high doses of phenothiazines can superimpose an atropine psychosis on a psychiatric illness. As far as possible atropine psychoses should be prevented rather than treated. Using benztropine or other antiparkinsonian agents at their minimal effective doses can do much to avoid them. Also phenothiazines and antidepressants should be used together only when both are clearly required. 5 references.

117584 Kurland, Leonard T. Department of Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN 55901 An appraisal of the neurotoxicity of cycad and the etiology of amyotrophic lateral sclerosis on Guam. ***Federation Proceedings.*** **31(5):1540-1542, 1972.**

The neurotoxicity of cycad and the etiology and epidemiology of amyotrophic lateral sclerosis and parkinsonism - dementia in Guam are discussed. Recent work on the effects of methylazoxymethanol acetate and cycasin are included. 26 references.

117598 Bucci, Luigi. Metropolitan Hospital, New York Medical College, New York, NY Drug-induced depression and tryptophan metabolism. ***Diseases of the Nervous System.*** **33(2):105-108, 1972.**

The hypothesis that a derangement of the tryptophan metabolism or of its metabolite serotonin may be pathologically responsible for the various categories of depression was tested. The forms of depression which occur during drug therapy are reviewed: 1) the psychotic, or endogenous depression; 2) the reactive or neurotic depression; 3) the involutional psychosis or melancholia. Cortisone, ACTH, oral contraceptives, and reserpine are reported to cause a more or less severe form of depression. The role of a derangement of the tryptophan metabolism, along with some other theoretical consideration, is briefly discussed. 26 references. (Author abstract)

117605 Moir, D.C.; Crooks, J.; Sawyer, P.; Turnbull, M.J.; Weir, R.D. Dept.of Pharmacology and Therapeutics, Univ.of Dundee, Dundee, Scotland Cardiotoxicity of tricyclic antidepressants. ***British Journal of Pharmacology (London).*** **44(2):371P-372P, 1972.**

A study of the cardiotoxicity of the tricyclic antidepressant amitriptyline was made with inpatients in a general hospital who were matched with a control group of inpatients. The association between administration of amitriptyline and sudden death in patients with cardiac disease has been confirmed. No increased incidence of sudden death was found in patients receiving amitriptyline without a diagnosis of cardiac disease or in cardiac patients whose amitriptyline was discontinued at least two weeks before death or discharge. The possible factors which might be contributing to the cardiotoxicity are: 1) interaction with concomitantly administered drugs; and 2) a decreased rate of drug metabolism resulting in increased plasma concentrations. 1 reference.

117674 no author. no address Barbiturates in asthma. ***British Medical Journal (London).*** **3(5825):490, 1972.**

The possibility that enzyme induction by phenobarbitone and other barbiturates adversely affects asthmatics receiving corticosteroids is in-

vestigated here. The effect of phenobarbitone was studied on 11 asthmatic patients on isotope labelled dexamethasone. The study showed increased asthmatic symptoms, deterioration of response in spirometric tests, and increased eosinophil counts when phenobarbitone was given and improvement after the drug was withdrawn when reduction of prednisone dosage was possible. Patients not dependent on steroids did not show similar changes during phenobarbitone treatment. Continual administration of phenobarbitone is therefore likely to reduce the therapeutic effect of corticosteriods in patients with asthma, and the prescribing of barbiturates might account for the need to increase the dosage of corticosteriods and cause the low plasma cortisol response which has been observed in some asthmatic patients. Further research is suggested on the extend and significance of enzyme induction in man and its therapeutic implications. 6 references.

16 METHODS DEVELOPMENT

108964 Kupferberg, Harvey Jerome. Applied Neurologic Research Branch, National Institute of Neurological Diseases and Stroke, NIH, Bethesda, Md. 20014 GLC determination of carbamazepine in plasma. *Journal of Pharmaceutical Sciences.* 61(2):284-286, 1972.

A gas - liquid chromatography (GLC) assay for carbamazepine (5H-dibenz(b,f)azepine-5-carboxamide), an anticonvulsant, in plasma is described. The procedure involves the selective extraction of carbamazepine from phenobarbital and diphenylhydantoin. Carbamazepine is stabilized for quantitation in GLC through the formation of its trimethylsilyl derivative. The sensitivity of the method is sufficient to quantitate blood levels in patients receiving carbamazepine for seizure disorders. 11 references. (Author abstract modified)

108967 Prue, D.G.; Warner, C.R.; Kho, B.T. Analytical Development Laboratory, Ayerst Laboratories Inc., Rouses Point, N.Y. 12979 Pulse polarographic determination of disulfiram. *Journal of Pharmaceutical Sciences.* 61(2):249-251, 1972.

A pulse polarographic method for the determination of bis (diethylthiocarbamoyl) disulfide (disulfiram) in tablets is described. Disulfiram has been used for treatment of alcoholism. It produces a sensitivity to alcohol by interfering with the normal metabolic degradation of alcohol in the body, resulting in an increased acetaldehyde concentration in the blood. The pulse polarographic method is more sensitive than d.c.polarography, and the peak -shape readout is inherently easier to identify and quantitate. An aqueous, ethanolic acetate buffer is used rather than the more commonly used aqueous, ethanolic ammonia buffer because interference by diethyldithiocarbamate is eliminated. A mechanism for the electrode process is proposed which involves reaction of the disulfiram with mercury drop to form the insoluble mercuric salt, which then undergoes reduction at the electrode surface. 11 references. (Author abstract modified)

108968 Kaistha, K.K.; Jaffe, Jerome H. Department of Psychiatry, University of Chicago, Chicago, Ill. 60637 Reliability of identification techniques for drugs of abuse in a urine screening program and drug excretion data. *Journal of Pharmaceutical Sciences.* 61(2):305-307, 1972.

Results of a double-blind study regarding the validation of extraction and identification techniques for abuse drugs in 50 control urines to which were added known concentrations of drugs are presented. Data on the excretion of some commonly abused drugs in human urine are also reported. Drugs studied were: morphine, codeine, methapyrilene, methadone, quinine, phenmetrazine, methamphetamine, amobarbital, phenobarbital, meperidine, secobarbital, amphetamine, pentobarbital, glutethimide, diphenylhydantoin, pentazocine, and alpha-acetylmethadol hydrochloride. 11 references. (Author abstract modified)

108969 McChesney, James D.; Beal, Deanna K.; Fox, Richard M. Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044 Rapid qualitative identification of barbiturates by mass spectrometry. *Journal of Pharmaceutical Sciences.* 61(2):310-312, 1972.

A rapid method of qualitative identification of barbituric acids, which does not require prior isolation of the barbiturate from the pharmaceutical dosage form, was developed utilizing mass spectrometry. This is achieved by the introduction of a portion of the powdered preparation directly into the mass spectrometer via the direct inlet system for solid samples and the fractional sublimation of the barbiturate by slowing increasing the solid inlet system temperature. The method is equally applicable to preparations of the sodium

salts of the barbiturates as to the free acids. Acids studied were: phenobarbital, butabarbital, amobarbital, hexobarbital, allobarbital, 5-allyl-5-isopropylbarbituric acid, and 5-allyl-5-phenylbarbituric acid. 6 references. (Author abstract modified)

113675 Ho, Beng T.; McIsaac, William M. Texas Research Institute of Mental Sciences, Texas Medical Center, Houston, Texas Brain chemistry and mental disease. New York, Plenum, 1972. 411 p. $17.50.

An integration of basic biochemical and pharmacological research, including clinical findings, the volume comprises the most current contributions in neurochemistry and psychopharmacology by active workers in the field. Representation is given to the most promising approaches in these areas, with the aim of increasing understanding of the etiology of mental disorders and hastening the development of more effective therapy. Highlights of the work include: new studies of schizophrenia and the affective disorders; genetic and metabolic fac tors associated with mental illness; developments in the application of chemotherapy to mental illness; a comprehensive review of the use of lithium in the treatment of mania; and a summary of the mechanisms of indoleamines and catecholamines and the drugs that affect the way they work.

114721 van Praag, H.M.; Korf, J.; Dols, L.C.W.; Schut, T. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands A pilot study of the predictive value of the probenecid test in application of 5-hydroxytryptophan as antidepressant. *Psychopharmacologia (Berlin).* 25(1):14-21, 1972.

A pilot study of the predictive value of the probenecid test in application of 5-hydroxytryptophan (5-HTP) as an antidepressant is presented. 5-HTP was for the first time given in large doses over a considerable period of time. In depressions, varying therapeutic effects have been obtained with 5-hydroxytryptamine (5-HT) precursors. This is possibly due to the fact that the group of the depressions is pathogenetically heterogeneous; that, specifically, some types do and other types do not entail disturbances in the central 5-HT metabolism; and that only the former types are precursor sensitive. This hypothesis was tested in a preliminary pilot study, and confirmed. The central 5-HT consumption was assessed on the basis of the probenecid test. 19 references. (Author abstract modified)

118794 Sullivan, Hugh R.; Blake, David A. Lilly Research Laboratories, Indianapolis, IN 46206 Quantitative determination of methadone concentrations in human blood, plasma and urine by gas chromatography. *Research Communications in Chemical Pathology and Pharmacology.* 3(3):467-478, 1972.

Blood and urine samples were collected from patients who had been receiving daily maintenance dosages of methadone. Using sodium hydroxide, the whole blood and plasma samples were adjusted to a pH of 9.5. The samples were then extracted twice with equivalent volumes of freshly distilled n-butyl chloride. The urine samples were similarly prepared, after which all samples were introduced into the gas chromatograph (GC). The GC column, which consisted of a siliconized glass U-tube packed with methylvinyl silicon gum rubber, was conditioned with heat and treated with Silyl 8 to prepare it for methadone analysis. The determination of the methadone present in the samples was accomplished via the use of the internal standard method; n-docosane was chosen as the internal standard. Using this method, methadone blood and plasma levels in patients receiving from 50 to 100mg of methadone daily have been determined. In addition, the concentrations of unchanged methadone and its two unconjugated basic metabolites in urine have been determined.2references

17 MISCELLANEOUS

107724 Ray, Oakley S. Department of Psychology, Vanderbilt University School of Medicine, Nashville, Tennessee Drugs, society, and human behavior. St.Louis, C.V.Mosby, 1972. 299 p.$5.95.

An analysis of human drug use aims at relating the fields of pharmacology, psychology, and history. It is noted that drug use is a part of American cultural history, and a major conclusion drawn is that the increase in drug use could be an integral part of the culture and that to eliminate it would require major changes in beliefs and attitudes. Specific sections deal with: an overview of drug use; the regulation of drug use; fundamentals -- the nervous system, pharmacology, the actions of drugs; the nondrug drugs -- alcohol, nicotine, caffeine, and over the counter drugs; psychotherapeutic drugs -- tranquilizers and mood modifiers, stimulants and depressants; the narcotic drugs; the phantasticants -- hallucinogens, marihuana and hashish.

108373 de Haen, Paul. Paul de Haen, Inc., New York, New York Golden years of drug introduction 1941 to 1970. *New York State Journal of Medicine.* 72(2):253-258, 1972.

Various types of drugs introduced during the years 1941-1970 are reviewed; adverse reactions are emphasized. Except for certain antibacterial agents, the other drugs, among the 917 introduced during this period, are essentially palliative, not curative. Among the drugs discussed are those for the relief of pain (narcotics, analgesics, and anesthetics), inflammatory disease, epilepsy, disorders of the psyche, and metabolic and endocrine disorders. Gains made and responsibilities of the future are discussed briefly.

108432 Bobon, Jean; Pinchard, Andre; Collard, Jackie; Bobon, Daniel P. Dept.of Psychiatry, University of Liege Medical School, Liege, Belgium Clinical classification of neuroleptics, with special reference to their antimanic, antiautistic, and ataraxic properties. *Comprehensive Psychiatry.* 13(2):123-131, 1972.

The tentative comparative physiognomy of neuroleptics put forward on a 5 parameter basis at the Fourth World Congress of Psychiatry in Madrid is developed and modified. Theoretical arguments and clinical experience support their new 6 parameter classification, namely, the ataraxic, antimanic, antiautistic, and antidelusional therapeutic parameters, and the extrapyramidal and adrenolytic side effects. 29 references. (Author abstract modified)

108886 Groover, Robert V. Pediatric Neurology, Mayo Clinic, Rochester, Minnesota The hyperkinetic child. *Psychiatric Annals.* 2(1):36-37, 41-44, 1972.

The excessive activity, behavioral and motor, of the hyperkinetic child is discussed. A short attention span and aimless activity suggest a delayed behavioral development compared to cognition abilities and age. Treatment involves parents, teachers, a restructured environment, and the judicious use of behavior modifying drugs. Stimulating situations, such as large children's parties, are contraindicated. Stimulants seem to be the most effective drugs. 15 references.

109002 Shimomura, Sam K. School of Pharmacy, University of California, San Francisco, Calif. Parkinsonism. *Journal of the American Pharmaceutical Association.* NS12(1):29-36, 1972.

Biochemical and therapeutic aspects of Parkinsonism are discussed. The parkinson patient is an ideal candidate for monitoring of drug therapy by the pharmacist on an outpatient basis. The diagnosis is known (the symptoms of parkinsonism are unmistakable) and the disease is chronic, so that the pharmacist will be able to come to know the patient and his problems from frequent contacts over many years. The drug therapy has a high potential for adverse drug reactions and drug interactions so that a knowledgeable and sympathetic pharmacist can significantly contribute to the long-term success of any treatment plan. 8 references. (Author abstract modified)

109291 no author. author address not given No more thorazine. *Medical Insight.* 4(2):60-61, 1972.

A Wisconsin circuit court judge ruled that a person has the right to refuse drugs during the customary 30 day observation period before commitment. The case involved a man who had received chlorpromazine against his will and who allegedly suffered adverse reactions as a result. The attorney of the state maintained that the administration of drugs during the observation period is authorized under the state legal code.

The judge differed with the defense attorney over the right of the patient to refuse drugs once he had been committed. The defense attorney stated that a patient has an inalienable right to refuse drugs whether he has been labelled committed or incompetent by the state, whereas the judge felt that drug treatment could be based on the hospital evaluation of the needs of the patient.

109295 Alexander, Leo; Berkeley, Austin W.; Cohen, Suzanne L. Tufts University Medical School Boston, Massachusetts Which antidepressant for which patient? *Medical Insight.* 4(2):12-19, 1972.

In a study of 735 cases of depression from 1956 to 1967, the relative effectiveness of several treatments for depression was compared in an actual clinical setting. Electroconvulsive therapy favored the recovery of the psychotic and borderline patients with depressions hinging on the issue of loss with guilt. Psychotherapy favored the neurotic patients. Tricyclic antidepressant medication appeared to affect all subcategories equally without differentiation. Monoamine oxidase inhibitors alone and meprobamate/benactyzine combination alone seemed to favor the neurotic depressions. 6 references.

111665 Daum, Conrad H.; Heinz, Bruce; Combs, Steve. Department of Community Medicine, University of Kentucky Medical Center, Lexington, Kentucky 40506 Prescription of psychotropic drugs in eastern Kentucky. *Journal of the Kentucky Medical Association.* 70(1):25-27, 1972.

A survey of patient visits to a sample of general practitioners in Eastern Kentucky showed a high frequency of phychiatric diagnoses. The rate of prescription of psychotrophic drugs was in keeping with this finding. 10 references. (Author abstract modified)

112117 Jaffe, Dennis T. Number 9, New Haven, Connecticut The repression and support of psychedelic experience. *American Journal of Orthopsychiatry.* 42(2):290, 1972.

A paper presented at the 49th annual meeting of the American Orthopsychiatric Association is summarized, providing a review of knowledge related to psychedelic drugs and describing current erroneous public response to them. Sociological theories by Szasz, Erikson, and Laing are introduced as hypotheses about processes that might show that the fear of psychedelics is due in part to projected fears of people, who see such drugs as freeing people from social controls and allowing the expression of impulses they fear in themselves. Certain values in American culture are shown to be antithetical to the kind of exploration of inner experience that psychedelics offer young people. In addition, suggestions are made as to how the experiences that young people are having with these drugs can be supported, while the adverse consequences of their drug use is mitigated. It is clear that current programs that focus on addiction and prevention of drug use are as unable to control drug use as prohibition was unable to end alcoholism. The thesis is that provision of a program that allows young people to go through their psychedelic experiences under the guidance of young people who themselves have been through them, controls most of the harmful effects found by research and prevents the accidental harm produced by using such drugs in bad situations. (Journal abstract modified)

112138 Freyhan, Fritz A. Department of Psychiatry, St.Vincent's Hospital and Medical Center of New York, New York Presidential address: the psychopathologist -- what man of science? *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p. (p.1-14).

The impact that the new science of psychopharmacology has had on the improvement of diagnosis is traced, along with a review of the development of the American Psychopathological Association and an analysis of Jaspers' concept of psychopathology in relation to science. Several methodological problems encountered by psychopathologists are reviewed, including the creation of statistically comparable groups, the contribution of clinical psychopathology to the discovery of psychoactive drug effects, understanding and intergrating clinical methods, matching procedures, and objectivity, reliability and validity. 12 references.

112144 Hippius, Hans. Free University of Berlin, Germany Pharmacogenic mood disorders. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p.(p.151-158).

The pathogenesis of mood disorders is discussed with emphasis on the question of whether and to what extent drugs are involved in the causation of mood disturbances. A survey of those groups of drugs noted as producing psychiatric side effects is reported, followed by a review of studies on depressive syndromes occur-

ring in the course of neuroleptic therapy. It is concluded that a closer analysis of so-called pharmacogenic depression shows that an investigation of the structure and development of syndromes can bring satisfactory results only when the drug is not considered as the single cause of the depression; therefore clinical research in psychiatry should consider all determining factors and apply a multifactorial approach. 23 references.

112145 Freedman, Alfred M. New York Medical College, New York /Pharmacogenic mood disorders./ Discussion of Dr.Hippius' paper. *In: Zubin, J., Disorders of mood.* Baltimore, Johns Hopkins Press, 1972. 200 p.(p.159-162).

Hippius' paper on pharmacogenic mood disorders is found to be important pragmatically with respect to the management of patients who are receiving drug therapy by giving insight into the action of drugs. It is noted to have theoretical value in delineating the multiplicity of factors that go into the genesis of mental illness. The phenomenon Hippius reports is concluded to require further work in view of the widespread occurrence of depressive symptoms in patients receiving neuroleptic drugs. 13 references.

112404 Serafetinides, E.A. Department of Psychiatry, University of California, Los Angeles, California Clinical judgment in psychopharmacology: discrepancies and their origin. *Psychiatric Opinion.* 9(1):31-33, 1972.

Problems encountered in making clinical judgments of the effectiveness of various psychopharmacological agents in treating mental disturbances are briefly discussed. It is reported that there are often discrepant ratings between psychiatrists and psychiatric nurses, and that those of psychiatrists less often tend to show changes as a result of psychotropic drug administration than those of nurses. Possible reasons for these discrepancies are discussed, noting that the 2 observers tend to rate 2 different sets of observations and also have different perspectives. The nurse is necessarily more administrative minded and tends to rate the patient's performance as a member of the ward, whereas the psychiatrist is more concerned with changes in personality and psychopathology. While psychotropic drugs may effect a symptomatic change, they seldom cure the core condition of mental illness. 5 references.

112426 Haward, L.R.C. Graylingwell Hospital, Chichester, Sussex, England Barbiturate-induced hypnosis: a golden jubilee review. *Bulletin of the British Psychological Society (London).* 25(86):23-24, 1972.

The advantages of using barbiturate induced hypnosis for treatment of various disturbances are briefly discussed and the historical evolution of this approach over the past 50 years is outlined. After many years of experience with barbiturate induced hypnosis, sufficient evidence of its values has been found. Benefits are: (1) when used by themselves, barbiturates produce similar sequelae to hypnosis including the release of emotional material; (2) they increase waking suggestibility; and (3) they make possible the induction of hypnosis in otherwise refractory patients. 17 references.

112626 Fraser, Mark S. author address not given Nocturnal enuresis. *Practitioner (London).* 208(1244):203-211, 1972.

An overview on treatment of nocturnal enuresis is presented. Topics include: some reasons for bedwetting; clinical types; avenues of treatment; scope of investigation; encouragement; psychiatric and social care; the rise of sedatives and tranquilizers, stimulants, vasopressin, and propantheline bromide; imipramine; the enuresis alarm; and a system of treatment. 30 references.

112627 Powell, B.W. author address not given Sleep disorders in childhood. *Practitioner (London).* 208(1244):198-202, 1972.

Sleep disorders in childhood are discussed. Topics include: normal sleep; bedtime problems; sleep rituals; waking in the night; medical conditions associated with sleep disturbance; management, and sedation. Chloral hydrate is the best drug for babies. Triclofos elixer, B.P.C.,antihistamines, promethazine and trimeprazine have been used in older children. 2 references.

112780 Zisook, Sidney. author address not given Ulcerative colitis: case responding to treatment with lithium carbonate. *Journal of the American Medical Association.* 219(6):755, 1972.

A letter to the editor presents a case in which a patient with ulcerative colitis was treated with lithium carbonate for his concomitant affective disorder. Both conditions have shown marked improvement, illustrating another possible area for

investigation concerning the therapeutic efficacy of lithium carbonate. 1 reference.

114078 Erenberg, Gerald. Montefiore Hospital, New York, N.Y. 10467 Mood-altering drugs and hyperkinetic children (continued). ***Pediatrics.*** **49(2):308-309, 1972.**

In a letter to the editor, the question of prescribing mood altering drugs to children with school behavior problems is examined. There are problems in identifying the child whose hyperactive behavior is due to minimal brain dysfunction. Medication with the cerebral stimulants may be helpful in controlling some cases of hyperactivity, but the degree of improvement and the duration of effectiveness is limited. Studies of the long-term effects of the drugs are necessary and should concern: social and educational adaptations of these children when they reach adolescence and adulthood; the mental health of the adult who was a hyperkinetic child. Treatment of hyperkinetic children should be handled on an individual basis and indiscriminant drugging of children reported to be misbehaving in school should be avoided. 14 references.

114079 Marks, Herman B. 225 Waterman St., Providence, R.I. 02906 Mood altering drugs and hyperkinetic children (continued). ***Pediatrics.*** **49(2):309-310, 1972.**

In a letter to the editor, the question of prescribing mood altering drugs for hyperkinetic children is examined. Although the medicated child is no longer a problem to teachers and parents, there is no evidence that either dextroamphetamine sulphate or methylphenidate hydrochloride has produced sustained improvement in learning. Many times children are hyperactive in school for reasons totally unrelated to minimal brain dysfunction. At the present time there are problems in making a diagnosis of either hyperkinetic syndrome or the minimal cerebral dysfunction syndrome, and a conservative philosophy in the use of psychotropic drugs is advised. 6 references.

114086 Brown, Walter A.; Manning, Tracey; Grodin, Jay. Box 1505-A, Yale Station, New Haven, Conn. 06520 The relationship of antenatal and perinatal psychologic variables to the use of drugs in labor. ***Psychosomatic Medicine.*** **34(2):119-127, 1972.**

Prenatal and perinatal psychologic variables related to sedative, analgesic and oxytosic administration in labor were investigated. Sixty four primigravidas were evaluated psychologically and medically throughout pregnancy and parturition. The relationship between psychological variables and the amounts of sedative and analgesic medication administration during labor were studied in 38 women with uncomplicated pregnancy and parturition. The correlates of oxytoxic administration were investigated in 22 additional women who received oxytoxics for induction or enhancement of labor. The amount of barbiturate administered during labor was negatively correlated with prenatal measures of psychologic adaptation. Similar relationships were found for meperidine administration. The use of these drugs was not related to psychologic variables measured during labor or to other perinatal variables, such as length of labor and time of hospital admission. Women who received oxytoxics were paired with women from the uncomplicated group who had the same obstetrician and similar course in labor. The oxytoxic group did not differ from the uncomplicated group on the prenatal psychologic variables. 12 references. (Journal abstract modified)

114540 Hirst, Donald V. Council Bluffs, Iowa Hazards of drug dependency. ***Journal of the American Medical Association.*** **219(12):1629, 1972.**

A letter to the editor commenting on use of barbiturates and tranquilizers for treatment of emotional tension, states that such treatments are particularly effective in dealing with patients in the chronic alarm state. However, if the patient is placed on such medication without treatment of the basic causes, he is indefinitely dependent on the medication and there is little hope of his becoming independent. If the medication is withdrawn the resulting emotional and physical reactions are a result of marked rebound in alarm tensions, not a pathologic effect of the medication itself. Such medication should not be withdrawn unless the patient is hospitalized, and there has been some understanding of the emotional tensions and the interaction and effects of the medication. 1 reference.

115076 Vesell, Elliot S. Dept.of Pharmacology, Milton S.Hershey Medical Center, Pennsylvania State Univ.College of Medicine, Hershey, PA 17033 Introduction: genetic and environmental factors af-

fecting drug response in man. *Federation Proceedings.* 31(4):125311269, 1972.

Large variation among individuals in rates of metabolism of many commonly used drugs is a relatively new area of research in pharmacogenetics; these variations are primarily under genetic control, negligibly influenced by environmental factors in most normal individuals not receiving drugs chronically and appear to be transmitted as polygenically controlled traits. Progress in pharmacogenetics has occurred recently as a result of intensive investigation of approximately 10 inborn errors of metabolism affecting enzymes that biotransform drugs in man. Most of these mutations are transmitted as single factors. Another area of current interest in pharmacogenetics concerns large individual differences in response to chronic administration of agents that induce or inhibit hepatic microsomal drug metabolizing enzymes. 59 references. (Author abstract)

115381 Wade, O.L.; Hood, H.E. University of Birmingham, Birmingham, England An analysis of prescribing of an hypnotic in the community. ***British Journal of Preventive and Social Medicine (London).*** **26(2):121-128, 1972.**

An analysis was made of the prescribing of an hypnotic preparation Mandrax (a compound containing methaqualone 250mg and diphenhydramine 25mg) in general practice in Northern Ireland between 1966 and 1970. There was an overall increase in the prescribing of Mandrax and by 1969 one quarter of all prescriptions for hypnotics were for this preparation. There were great variations from practice to practice, ranging from no prescribing of Mandrax at all in some practices to the prescribing of more than 4000 tablets per 1000 patients per month in others. There were marked geographical variations in the prescribing of Mandrax, less being prescribed in rural and western areas than in Belfast and its environs. Doctors who became frequent prescribers of the drug tended to continue to be frequent prescribers throughout the survey. It is suggested that these results are typical of the life cycle of a newly introduced pharmaceutical preparation and that these cycles of popularity may be expressions of expectations of effectiveness of drugs which can never be achieved. 4 references. (Author abstract)

115967 Bowers, Malcolm B., Jr.; Van Woert, Melvin H. Yale University, New Haven, CT Sexual behavior during L-dopa treatment of Parkinson's disease. ***Medical Aspects of Human Sexuality.*** **6(7):88, 91, 95-96, 98, 1972.**

The effects of L-dihydroxyphenylalanine (L-dopa), used in the treatment of Parkinson's disease, on sexual behavior are discussed. A number of studies on the subject reveal mixed effects. Sexual feeling and function were evaluated in a group of 19 parkinsonian patients who had received L-dopa for 3 to 15 months. The interviews focused on possible side-effects that patients had experienced while taking L-dopa, specifically, alterations in sleep and appetite, as well as effects on sexual behavior. The patients studied could be grouped into three general patterns: overall improvement in function, with attendant psychosocial consequences; seemingly specific stimulation of sexual drive independent of overall functional improvement; and loss of sexual inhibitions in patients who developed hypomanic reactions or acute brain syndromes while taking L-dopa. Results suggest that reports of activation of sexual behavior in parkinsonian patients taking L-dopa are relatively common. L-dopa appears to cause a transient specific stimulation of sexual drive in only a small percentage of patients. The increase in sexual drive may not be associated with more satisfactory sexual performance. The study underscores the complexity and individuality of response to a pharmacologic influence on human sexual behavior. Dopamine, the catecholamine metabolite of L-dopa, may influence sexual function in animals. The relationship, if any, of animal experiments to sexual behavior during L-dopa treatment of parkinsonian patients is open to question. 11 references.

116024 Rittelmeyer, Louis F. Department of Psychiatry, Georgetown University Medical School, Washington, DC On prescribing tranquilizers. ***Medical Annals of the District of Columbia.*** **41(4):251-252, 1972.**

The classification of tranquilizers into major and minor categories is presented for the benefit of the medical student. The major group, consisting of the phenothiazine and rauwolfia derivatives, are characterized by: the production of emotional calmness with relatively little sedation, even in disturbed psychotic patients; reversible extrapyramidal symptoms and other toxic reactions, and little or no dependency or habituation. The minor tranqulizers, of which meprobamate and chlordiazepoxide (Librium) are representa-

tive, do not produce a calming effect of the same quality as that of the major tranquilizers and are relatively ineffective in psychotic disorders. They have a low incidence of side effects but may be addictive. Barbiturates and alcohol also possess some properties of the minor group. The proper use of tranquilizers requires an understanding of the principle that the patient should be at a level to permit alertness but not so high as to permit pain or so low as to impair functioning.

116702 Merlis, Sidney; Sheppard, Charles; Fracchia, John. Division of Psychiatric Research, Central Islip State Hospital, Central Islip, NY Psychiatrists' characteristics and polypharmacy. ***Canadian Psychiatric Association Journal (Ottawa).*** **17(Special Supplement 2):89-92, 1972.**

A panel discussion delivered at the thirteenth annual meeting of the G.W.A.N.Psychiatric Research Society is presented, in which results of a study undertaken to obtain data as to the extent to which polypharmacy might be selected as the initial therapeutic modality in psychiatric disease with an acute onset are reported. A questionnaire which included a case history designed to elicit treatment preferences in psychiatric disease was distributed to psychiatrists on the staffs of 17 state mental hospitals in New York State. Results of the survey, based upon a 45%return, indicate that two of every five respondents selected polypharmacy as the preferred initial treatment regimen for the hypothetical patient described in the questionnaire. Recency of training (residency completion) and fewer private agency affiliations appeared to be the major characteristic of the psychiatrists in this sample, who tended to employ drug combinations. These data are interpreted as being consistent with the hypothesis that polypharmacy may currently be in vogue as a therapeutic modality despite the lack of a clear cut rationale for its use or proof of its efficacy. 4 references. (Author abstract modified)

116762 Bonny, Helen L.; Pahnke, Walter N. Maryland Psychiatric Research Center, Baltimore, MD The use of music in psychedelic (LSD) psychotherapy. ***Journal of Music Therapy.*** **9(2):64-87, 1972.**

The use of music in psychedelic (lysergic acid diethylamide - LSD) psychotherapy is discussed. The five ways in which music complements therapeutic objectives are discussed: (1) by helping the patient relinquish usual controls and enter more fully into his inner world of experience; (2) by facilitating the release of intense emotionality; (3) by contributing toward a peak experience; (4) by providing continuity in an experience of timelessness; and (5) by directing and structuring the experience. A discussion of how music is used in psychedelic drug sessions includes a music experience questionnaire and a description of the six phases of the LSD experience with suggested musical selections for each phase. Insights are given on the use of music in drug assisted therapy which may apply to nondrug therapy. 18 references.

117460 Prien, Robert F. Department of Medicine and Surgery, Veterans Administration, Washington, DC 20420 Chronic organic brain syndrome: a review of the therapeutic literature with special emphasis on chemotherapy. Washington, D.C., Veterans Administration, 1972. 29 p.

The therapeutic literature on chronic organic brain syndrome is reviewed with special emphasis on chemotherapy. Topics presented are: description and types of organic brain syndrome; therapeutic attitude and treatment; method of assessment; nonsomatic therapies; psychotropic drugs; cerebral vasodilators; ergot alkaloids (Hydergine); anticoagulants; central nervous system stimulants; miscellaneous agents; and implications for chemotherapeutic research. A classification of drugs is presented as an appendix. 201 references.

117656 Smith, Stephen E. St.Thomas's Hospital Medical School, London, England Drugs and the mental state. ***Nursing Times (London).*** **68(32):1001-1002, 1972.**

The present state of knowledge of the biochemical and physiological mechanisms of drugs as related to mental disorders is briefly reviewed here. Many drugs have different effects on different patients according to their existing mental state and sometimes according to their age. Thus, barbiturates produce sedation in most people, but they tend to make old people confused and sometimes violent. The effects and biochemical and physiological mechanisms of general stimulants, antidepressants, psychotomimetics, general depressants, and tranquillizers are briefly reviewed. Further research is needed on the way these drugs act, about the physiological basis of the mind, and on the underlying disturbances of mental disorders.

Specific emphasis should be placed on studies of mood and amine levels in the brain.

117943 DiMascio, Alberto. no address Psychotropic drug overuse: an examination of prescription practices. *Massachusetts Journal of Mental Health.* 2(3):25-38, 1972.

The efficient prescribing of psychotropic drugs is discussed. It is common in clinical psychiatry to prescribe psychotropic drugs so that the total daily amount is administered in equally divided doses given three to six times daily, the drug is given every day of the week and without interruption or change for years. Antiparkinson drugs are initiated with and sustained as long as an antipsychotic drug is given. These common practices do not rest on any scientific basis, and they may result in a greater incidence of side effects than alternate procedures. They most certainly are costlier than alternate procedures. Research has shown the following facts basic to effective, economic drug prescribing practices: 1) psychotropic drugs, in general have a long half life; 2) the metabolism of psychotropic drugs and their excretion proceed at a very slow rate; 3) these drugs and their metabolites accumulate in various body tissues with continued drug administration until a saturation level is achieved and on cessation of the drugs, the tissues release these accumulations very slowly; 4) the appearance of the pharmacological properties of primary clinical value in psychiatry is noted later in time than are the secondary properties or side effects. All these facts are relevant not only to antipsychotic drugs but also to antidepressant and antianxiety drugs. 28 references.

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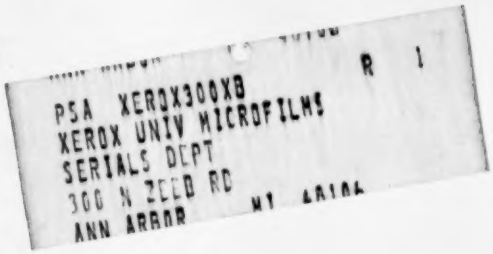

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